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Registration Standard: Products Containing 4-Aminopyridine, Avitrol (Trade Name)

(U.S.) Environmental Protection Agency
Washington, DC

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REGISTRATION STANDARD:
PRODUCTS CONTAINING

4-Aminopyridine
(Avitrol®)

ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDE PROGRAMS

Washington, DC 20460

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I. HOW TO REGISTER UNDER A REGISTRATION STANDARD

Organization of the Standard
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Organization of the Standard

This first chapter explains the purpose of a Registration Standard and summarizes the legal principles involved in registering or re-registering under a Standard. The second chapter sets forth the requirements that must be met to obtain or retain registration for products covered by this particular Registration Standard. In the remaining chapters, the Agency reviews the available data by scientific discipline, discusses the Agency's concerns with the identified potential hazards, and logically develops the conditions and requirements that would reduce those hazards to acceptable levels.

Purpose of the Standard

Section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) provides that "no person in any State may distribute, sell, offer for sale, hold for sale, ship, deliver for shipment, or receive (and having so received) deliver or offer to deliver, to any person any pesticide which is not registered with the Administrator [of EPA]." To approve the registration of a pesticide, the Administrator must find, pursuant to Section 3(c)(5) that:

"(A) its composition is such as to warrant the proposed claims for it;
(B) its labeling and other material required to be submitted comply with the requirements of this Act;
(C) it will perform its intended function without unreasonable adverse effects on the environment; and
(D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."

In making these findings, the Agency reviews a wide range of data which registrants are required to submit, and assesses the risks and benefits associated with the use of the proposed pesticide. But the established approach to making these findings has been found to be defective on two counts:

First, EPA and its predecessor agency, the United States Department of Agriculture (USDA), routinely reviewed registration applications on a 'product by product' basis, evaluating each product-specific application somewhat independently. In the review of products containing similar components, there was little opportunity for a retrospective review of the full range of pertinent data available in Agency files and in the public literature. Thus the 'product by product' approach was often inefficient and sometimes resulted in inconsistent or incomplete regulatory judgments.

Second, over the years, as a result of inevitable and continuing advances in scientific knowledge, methodology, and policy, the data base for many pesticides came to be considered inadequate by current scientific and regulatory standards. Given the long history of pesticide regulation in several agencies, it is even likely that materials may have been lost from the data files. When EPA issued new requirements for registration in 1975 (40 CFR 162) and proposed new guidelines for hazard testing in 1978 (43 FR 29686, July 10, 1978 and 43 FR 37336, August 2, 1978), many products that had already been registered for years were being sold and used without the same assurances of human and environmental safety as was being required for new products. Because of this inconsistency, Congress directed EPA to re-register all previously registered products, so as to bring their registrations and their data bases into compliance with current requirements [See FIFRA Section 3(g)].

Facing the enormous job of re-reviewing and calling-in new data for the approximately 35,000 current registrations, and realizing the inefficiencies of the 'product by product' approach, the Agency decided that a new, more effective method of review was needed.

A new review procedure has been developed. Under it, EPA publishes documents called Registration Standards, each of which discusses a particular pesticide active ingredient. Each Registration Standard summarizes all the data available to the Agency on a particular active ingredient and its current uses, and sets forth the Agency's comprehensive position on the conditions and requirements for registration of all existing and future products which contain that active ingredient. These conditions and requirements, all of which must be met to obtain or retain full registration or re-registration under Section 3(c)(5) of FIFRA, include the submission of needed scientific data which the Agency does not now have, compliance with standards of toxicity, composition, labeling, and packaging, and satisfaction of the data compensation provisions of FIFRA Section 3(c)(1)(D).

The Standard will also serve as a tool for product classification. As part of the registration of a pesticide product, EPA may classify each product for "general use" or "restricted use" [FIFRA Section 3(d)]. A pesticide is classified for "restricted use" when some special regulatory restriction is needed to ensure against unreasonable adverse effects to man or the environment. Many such risks of unreasonable adverse effects can be lessened if expressly-designed label precautions are strictly followed. Thus the special regulatory restriction for a "restricted use" pesticide is usually a requirement that it be applied only by, or under the supervision of, an applicator who has been certified by the State or Federal government as being competent to use pesticides safely, responsibly, and in accordance with label directions. A restricted-use pesticide can have other regulatory restrictions [40 CFR 162.11(c)(5)] instead of, or in addition to, the certified applicator requirement. These other regulatory restrictions may include such actions as seasonal or regional limitations on use, or a requirement for the monitoring of residue levels after use. A pesticide classified for "general use," or not classified at all, is available for use by any individual who is in compliance with State or local regulations. The Registration Standard review compares information about potential adverse effects of specific uses of the pesticide with risk criteria listed in 40 CFR 162.11(c), and thereby determines whether a product needs to be classified for "restricted use." If the Standard does classify a pesticide for "restricted use," this determination is stated in the second chapter.

Requirement to Re-register Under the Standard

FIFRA Section 3(g), as amended in 1978, directs EPA to re-register all currently registered products as expeditiously as possible. Congress also agreed that re-registration should be accomplished by the use of Registration Standards.

Each registrant of a currently registered product to which this Standard applies, and who wishes to continue to sell or distribute his product in commerce, must apply for re-regisration. His application must contain proposed labeling that complies with this Standard.

EPA will issue a notice of intent to cancel the registration of any currently registered product to which this Standard applies if the registrant fails to comply with the procedures for re-registration set forth in the Guidance Package which accompanies this Standard.

"Product Specific" Data and "Generic" Data

In the course of developing this Standard, EPA has determined the types of data needed for evaluation of the properties and effects of products to which the Standard applies, in the disciplinary areas of Product Chemistry, Environmental Fate, Toxicology, Residue Chemistry, and Ecological Effects. These determinations are based primarily on the data Guidelines proposed in 1978 (43 FR 29686, July 10, 1978, and 43 FR 37336, August 2, 1978), as applied to the use patterns of the products to which this Standard applies. Where it appeared that data from a normally applicable Guidelines requirement was actually unnecessary to evaluate these products, the Standard indicates that the requirement has been waived. On the other hand, in some cases studies not required by the Guidelines may be needed because of the particular composition or use pattern of products the Standard covers; if so, the Standard explains the Agency's reasoning. Data guidelines have not yet been proposed for the Residue Chemistry discipline, but the requirements for such data have been in effect for some time and are, the Agency believes, relatively familiar to registrants. Data which we have found are needed to evaluate the registrability of some products covered by the Standard may not be needed for the evaluation of other products, depending upon the composition, formulation type, and intended uses of the product in question. The Standard states which data requirements apply to which product categories. (See the second chapter.)

The various kinds of data normally required for registration of a pesticide product can be divided into two basic groups:

(A) data that is "product specific," i.e., data that relates only to the properties or effects of a product with a particular composition (or a group of products with closely similar composition); and

(B) "generic" data that pertains to the properties or effects of a particular ingredient, and thus is relevant to an evaluation of the risks and benefits of all products containing that ingredient (or all such products having a certain use pattern), regardless of any such product's unique composition.

The Agency requires certain "product specific" data for each product to characterize the product's particular composition and physical/chemical properties (Product Chemistry), and to characterize the product's acute toxicity (which is a function of its total composition). The applicant for registration or re-registration of any product, whether it is a manufacturing-use or end-use product, and without regard to its intended use pattern, must submit or cite enough of this kind of data to allow EPA to evaluate the product. For such purposes, "product specific" data on any product other than the applicant's is irrelevant, unless the other product is closely similar in composition to the applicant's. (Where it has been found practicable to group similar products for purposes of evaluating, with a single set of tests, all products in the group, the Standard so indicates.) "Product specific" data on the efficacy of particular end-use products is also required where the exact formulation may affect efficacy and where failure of efficacy could cause public health problems.

All other data needed to evaluate pesticide products concerns the properties or effects of a particular ingredient of products (normally a pesticidally active ingredient, but in some cases a pesticidally inactive, or "inert," ingredient). Some data in this "generic" category are required to evaluate the properties and effects of all products containing that ingredient [e.g., the acute LD-50 of the active ingredient in its technical or purer grade; see proposed 40 CFR 163.81-1(a), 43 FR 37355].

Other "generic" data are required to evaluate all products which both contain a particular ingredient and are intended for certain uses (see, e.g., proposed 40 CFR 163.82-1, 43 FR 37363, which requires subchronic oral testing of the active ingredient with respect to certain use patterns only). Where a particular data requirement is use-pattern dependent, it will apply to each end-use product which is to be labeled for that use pattern (except where such end-use product is formulated from a registered manufacturing-use product permitting such formulations) and to each manufacturing-use product with labeling that allows it to be used to make end-use products with that use pattern. Thus, for example, a subchronic oral dosing study is needed to evaluate the safety of any manufacturing-use product that legally could be used to make an end-use, food-crop pesticide. But if an end-use product's label specified it was for use only in ways that involved no food/feed exposure and no repeated human exposure, the subchronic oral dosing study would not be required to evaluate the product's safety; and if a manufacturing-use product's label states that the product is for use only in making end-use products not involving food/feed use or repeated human exposure, that subchronic oral study would not be relevant to the evaluation of the manufacturing-use product either.

If a registrant of a currently registered manufacturing-use or end-use product wishes to avoid the costs of data compensation [under FIFRA Section 3(c)(1)(D)] or data generation [under Section 3(c)(2)(B)] for "generic" data that is required only with respect to some use patterns, he may elect to delete those use patterns from his labeling at the time he re-registers his product. An applicant for registration of a new product under this Standard may similarly request approval for only certain use patterns.

Data Compensation Requirements under FIFRA 3(c)(1)(D)

Under FIFRA Section 3(c)(1)(D), an applicant for registration, re-registration, or amended registration must offer to pay compensation for certain existing data the Agency has used in developing the Registration Standard. The data for which compensation must be offered is all data which is described by all the following criteria:

(1) the data were first submitted to EPA (or to its predecessor agencies, USDA or FDA), on or after January 1, 1970;
(2) the data were submitted to EPA (or USDA or FDA) by some other applicant or registrant in support of an application for an

experimental use permit, an amendment adding a new use to a registration, or for re-registration, or to support or maintain in effect an existing registration;

(3) the data are relevant to the Agency's decision to register or re-register the applicant's product under the Registration Standard, taking into account the applicant's product's composition and intended use pattern(s);

(4) the data are determined by EPA to be valid and usable in reaching regulatory conclusions; and

(5) the data are not those for which the applicant has been exempted by FIFRA Section 3(c)(2)(D) from the duty to offer to pay compensation. (This exemption applies to the "generic" data concerning the safety of an active ingredient of the applicant's product, not to "product specific" data. The exemption is available only to applicants whose product is labeled for end-uses for which the active ingredient in question is present in the applicant's product because of his use of another registered product containing that active ingredient which he purchases from another producer.)

An applicant for re-registration of an already registered product under this Standard, or for registration of a new product under this Standard, accordingly must determine which of the data used by EPA in developing the Standard must be the subject of an offer to pay compensation, and must submit with his application the appropriate statements evidencing his compliance with FIFRA Section 3(c)(1)(D).

An applicant would never be required to offer to pay for "product specific" data submitted by another firm. In many, if not in most cases, data which are specific to another firm's product will not suffice to allow EPA to evaluate the applicant's product, that is, will not be useful to the Agency in determining whether the applicant's product is registrable. There may be cases, however, where because of close similarities between the composition of two or more products, another firm's data may suffice to allow EPA to evaluate some or all of the "product specific" aspects of the applicant's product. In such a case, the applicant may choose to cite that data instead of submitting data from tests on his own product, and if he chooses that option, he would have to comply with the offer-to-pay requirements of Section 3(C)(1)(D) for that data.

Each applicant for registration or re-registration of a manufacturing-use product, and each applicant for registration or re-registration of an end-use product, who is not exempted by FIFRA Section 3(c)(2)(D), must comply with the Section 3(c)(1)(D) requirements with respect to each item of "generic" data that relates to his product's intended uses.

A detailed description of the procedures an applicant must follow in applying for re-registration (or new registration) under this Standard is found in the Guidance Package for this Standard.

Obtaining Data to Fill "Data Gaps"; FIFRA 3(c)(2)(B)

Some of the kinds of data EPA needs for its evaluation of the properties and effects of products to which this Standard applies have never been submitted to the Agency (or, if submitted, have been found to have deficiencies rendering them inadequate for making registrability decisions) and have not been located in the published literature search that EPA conducted as part of preparing this Standard. Such instances of missing but required data are referred to in the Standard as "data gaps".

FIFRA Section 3(c)(2)(B), added to FIFRA by the Congress in 1978, authorizes EPA to require registrants to whom a data requirement applies to generate (or otherwise produce) data to fill such "gaps" and submit those data to EPA. EPA must allow a reasonably sufficient period for this to be accomplished. If a registrant fails to take appropriate and timely steps to fill the data gaps identified by a section 3(c)(2)(B) order, his product's registration may be suspended until the data are submitted. A mechanism is provided whereby two or more registrants may agree to share in the costs of producing data for which they are both responsible.

The Standard lists, in its summary second chapter, the "generic" data gaps and notes the classes of products to which these data gaps pertain. The Standard also points out that to be registrable under the Standard, a product must be supported by certain required "product specific" data. In some cases, the Agency may possess sufficient "product specific" data on one currently registered product, but may lack such data on another. Only those Standards which apply to a very small number of currently registered products will attempt to state definitively the "product specific" data gaps on a 'product by product' basis. (Although the Standard will in some cases note which data that EPA does possess would suffice to satisfy certain "product specific" data requirements for a category of products with closely similar composition characteristics.)

As part of the process of re-registering currently registered products, EPA will issue Section 3(c)(2)(B) directives requiring the registrants to take appropriate steps to fill all identified data gaps -- whether that data in question is "product specific" or "generic" -- in accordance with a schedule.

Persons who wish to obtain registrations for new products under this Standard will be required to submit (or cite) sufficient "product specific" data before their applications are approved. Upon registration, they will be required under Section 3(c)(2)(B) to take appropriate steps to submit data needed to fill "generic" data gaps. (We expect they will respond to this requirement by entering into cost-sharing agreements with other registrants who previously have been told they must furnish the data.) The Guidance Package for this Standard details the steps that must be taken by registrants to comply with Section 3(c)(2)(B).

Amendments to the Standard

Applications for registration which propose uses or formulations that are not presently covered by the Standard, or which present product compositions, product chemistry data, hazard data, toxicity levels, or labeling that do not meet the requirements of the Standard, will automatically be considered by the Agency to be requests for amendments to the Standard. In response to such applications, the Agency may request additional data to support the proposed amendment to the Standard, or may deny the application for registration on the grounds that the proposed product would cause unreasonable adverse effects to the environment. In the former case, when additional data have been satisfactorily supplied, and providing that the data do not indicate the potential for unreasonable adverse effects, the Agency will then amend the Standard to cover the new registration.

Each Registration Standard is based upon all data and information available to the Agency's reviewers on a particular date prior to the publication date. This "cut-off" date is stated at the beginning of the second chapter. Any subsequent data submissions and any approved amendments will be incorporated into the Registration Standard by means of addenda, which are available for inspection at EPA in Washington, D.C., or copies of which may be requested from the Agency. When all the present "data gaps" have been filled and the submitted data have been reviewed, the Agency will revise the Registration Standard. Thereafter, when the Agency determines that the internally maintained addenda have significantly altered the conditions for registration under the Standard, the document will be updated and re-issued for publication.

While the Registration Standard discusses only the uses and hazards of products containing the designated active ingredient(s), the Agency is also concerned with the potential hazards of some inert ingredients and impurities. Independent of the development of any one Standard, the Agency has initiated the evaluation of some inert pesticide ingredients. Where the Agency has identified inert ingredients of concern in a specific product to which the Standard applies, these ingredients will be pointed out in the Guidance Package.

II. Regulatory Position

This chapter presents the Agency's decision on what Standards of product composition, toxicity, use, labeling, and packaging are required for the pesticide active ingredient in question. The decision complies with the rules and regulations (40 CFR 162) used to implement the Federal Insecticide, Fungicide, and Rodenticide Act, as amended (FIFRA), and with the Agency's present regulatory policies. There are different requirements for manufacturing-use chemicals and for each type of end-use formulation which present a significantly different set of hazards. This Registration Standard is based upon all data and information on 4-aminopyridine available to the Agency's reviewers as of December 28, 1979.

Two companies have submitted data in support of their registration of 4-aminopyridine products: Phillips Petroleum Company of Bartlesville, Okla. and Avitol Corporation of Tulsa, Okla. These data may be cited by other registrants or applicants for registration, when appropriate, to support the registration(s) of their own product(s) provided they have offered and agreed to pay compensation as required by FIFRA Sections 3(c)(1)(d) and 3(c)(2)(d). Anyone wishing to cite data submitted by Avitrol Corporation or Phillips Petroleum Company must offer and agree to pay compensation to Avitrol Corporation since Phillips Petroleum Company sold all 4-aminopyridine registration rights to Avitrol Corporation in 1972 and has requested not to receive compensation offers.

Manufacturing-Use

The Agency has reviewed all data available to it. Although incomplete, these data indicate that manufacturing-use 4aminopyridine is suitable for registration because it does not meet or exceed the risk criteria leading to a Rebuttable Presumption Against Registration [Chapter 40, Section 162.119a) of the Code of Federal Regulations]. Data gaps have been identified; when these data are supplied, the Agency will again review the registration status of this compound.

In order to be covered under this Standard, a manufacturing-use 4-aminopyridine product must comply with the following standards. A manufacturing-use 4-aminopyridine product must contain 4-aminopyridine as an active ingredient. Intentionally added inerts present in quantities greater than 0.10%, by weight of the total product, must consist of food or feedstuffs only. Manufacturing-use 4-aminopyridine products may fall into Toxicity Categories I through IV for the following acute effects:

Acute Oral Toxicity;

Acute Dermal Toxicity;

Acute Inhalation Toxicity;

Primary Eye Irritation; and

Primary Dermal Irritation

Labels for manufacturing-use products must include the following:

1. The intended end-use of products formulated from manufacturing-use products must be stated on the manufacturing-use products' labels. All manufacturing-use 4-aminopyridine products must therefore carry the following statement on the label: For Formulation into End-Use Products Intended only for Bird Control.

2. All manufacturing-use 4-aminopyridine products must carry the following warning on the label, under the "Hazards to Wildlife" section:

> This pesticide is toxic to birds and fish. Do not discharge into lakes, streams, ponds or public water unless in accordance with an NPDES permit. For guidance contact your Regional Office of the EPA.

3. All manufacturing-use 4-aminopyridine products must carry the following statement of practical treatment on the label.

> If swallowed:
> If the patient is unconscious, maintain breathing and heartbeat (CPR: cardiopulmonary resuscitation). Contact your local Poison Control Center, hospital or physician immediately.
>
> If patient is conscious, induce vomiting with syrup of ipecac (if not available stimulate the back of the throat with finger). Never give anything by mouth to an unconscious person. Contact your local Poison Control Center, hospital or physician immediately.

4. Manufacturing-use product labels must comply with the requirements of 40 CFR 162.10 regarding toxicity hazard warnings, first aid statements, and label format, including placement of hazard warnings on the label, type size and color, etc.

To be covered under this Standard, all applicants for registration or re-registration of technical and formulation intermediate products must agree to cite or submit the following information on the physical/chemical composition of each proposed product. Listed after each data gap is the section of of the Proposed Guidelines which describes that type of data and when it is required [43 FR, No. 132, 29696 of July 10, 1978; and 43 F, No. 163, 37336 of August 22, 1978].

Product Chemistry	Guideline Section
For All Manufacturing-Use Products	
1. Density or specific gravity	163.61-8(c)(8)
For Technical	
2. Chemical Idenity Process	163.61-3
4. Product Analytical Methods and Data	163.61-7
5. Solubility	163.61-8(c)(4) 6
6. Octanol/Water Partition Co-efficient	163.61-8(c)(6)
7. pH-Aqueous solution	163.61-8(c)(11)

4-Aminopyridine Formulations

In order to be covered under this Standard, an end-use, ready-to-use bait or dust 4-aminopyridine product must contain 4-aminopyridine as an active ingredient. All 4-aminopyridine ready-to-use bait and dust products, regardless of the Toxicity Categories assigned for acute effects, are classified as restricted use pesticides and must consequently bear the label statement: "For sale to and use only by Certified Applicators or persons under their direct supervision."

In addition, 4-aminopyridine formulated products must comply with the following standards.

Ready-to-use Baits

1. Intentionally added inerts present in quantities greater than 0.10%, by weight of the total product, must consist of food or feedstuffs only.
2. When registered for use in agricultural crops, the product must not exceed 0.03%, by weight of the total product, 4-aminopyridine. The product may consist of 3.0% or less 4-aminopyridine per treated granule if it is diluted, prior to packaging, at a ratio of 1 treated granule to 99 untreated granules.

3. When registered for the control of house sparrows, cowbirds, blackbirds, or pigeons at nesting and roosting structures, the product must not exceed 0.5% by weight of the total product, 4-aminopyridine.
4. When registered for the control of crows at nesting and roosting structures or for the control of starlings in cattle feedlots, the product must not exceed 1.0% by weight of the total product, 4-aminopyridine.

Dust

1. Intentionally added inerts must consist of food or feedstuffs only.
2. When registered for the control of herring gulls at nesting and roosting structures and at sanitary landfills, the product must not exceed 25% by weight of 4-aminopyridine.
3. When registered for the control of starlings in cattle feedlots, the product must not exceed 50% by weight of 4-aminopyridine.

Labels for 4-aminopyridine formulated products must include the following:

1. All 4-aminopyridine formulated products must bear the following statement of practical treatment on the front panel of the label:

> If swallowed:
> If the patient is unconscious, maintain breathing and heartbeat (CPR: cardiopulmonary resuscitation). Contact your local Poison Control Center, hospital or physician immediately.
>
> If patient is conscious, induce vomiting with syrup of ipecac (if not available stimulate the back of the throat with finger). Never give anything by mouth to an unconscious person! Contact your local Poison Control Center, hospital or physician immediately.

2. Each 4-aminopyridine formulated product must carry on the label toxicity hazard warnings and first aid statements appropriate to the Toxicity Categories assigned to that product for acute effects [refer to 40 CFR 162.10] with the following exception. If registrants of 4-aminopyridine dust products do not agree to provide or cite data on the teratogenic or mutagenic potential of 4-aminopyridine [Refer to Toxicology Chapter], all 4-aminopyridine dust products,

regardless of the Toxicity Categories assigned for acute inhalation toxicity and acute dermal toxicity, must require applicators to wear protective clothing including long sleeves, gloves, and respirators.

3. 4-aminopyridine formulated products must include the following warnings under the "Hazards to Wildlife" section:

a. For all products
This product is toxic to birds and fish. Do not contaminate water by cleaning of equipment or disposal of wastes.

b. For products intended for use in agricultural crops. Do not allow bait to remain in unprotected places after control measures are completed.

c. For ready-to-use bait products containing greater than 3.0% (per treated granule) 4-aminopyridine and all dust products.
Pick up and dispose of dead birds by burial.

4. All 4-aminopyridine formulated products must include the following under the section for Use Restrictions:

a. For all products
Before application in your area, consult endangered species personnel of the U.S. Fish and Wildlife Service to ensure that endangered and rare bird species are not likely to be adversely affected by use of this product.

b. For all products except those intended for the control of herring gulls
Investigate local laws that may prohibit the use of any toxic chemical in bird control.

For all products
[product name] is a poison with flock-alarming properties used for control of (type of birds) in such a way that a part of a flock may react and frighten the rest away. Birds that react and alarm a flock usually die.

Do not use where food (grain or meat) might become contaminated.

d. For all products intended for use in agricultural crops

This product must be applied in accordance with 40 CFR Part 170.

Registrants may amplify the above statement on labels or labeling by stating the requirements of 40 CFR Part 170 or additions thereto if they choose.

e. For pretreated baits
Do not feed to livestock or poultry.
Do not mix with grain for livestock or poultry.

f. For dust products
Keep away from livestock, poultry, and pets.

g. For products intended for use in cattle feedlots
Keep baits off the ground, out of reach of cattle.

5. All formulated 4-aminopyridine products must specify all prebaiting methods on the label, under the section "Prebaiting Directions". If the product is intended for use at sanitary landfills or at target species' nesting and roosting sites, the directions must include the following statement.

> This product must not be applied where nontarget birds feed. Careful observation of the birds' feeding habits must therefore be made to establish proper feeding locations and to determine that no nontarget birds are feeding on the prebait.

6. All 4-aminopyridine ready-to-use bait products intended for use in agricultural crops must specify all application methods and rates on the label, under the section "Baiting Directions." Baiting directions must include the following statement:

> Confine treatment to areas 50 feet in from field edge.

No application rate in excess of .0144 ounces 4-aminopyridine per acre on the portion being treated may be recommended. Directions may not recommend more than four applications per crop season for corn or more than five applications per crop season for sunflowers.

If the product is intended for use at sanitary landfills, cattle feedlots, or nesting and roosting sites, baiting directions must include the following:

> To obtain minimal mortality the distribution of [PRODUCT NAME] should be limited to scattered spot placements that will provide feeding opportunities only for the necessary number of target birds. After the birds' feeding pattern has been established through prebaiting, replace untreated bait with diluted treated bait only at sites where target birds are actively feeding. Do not apply treated bait to inactive feeding sites. Pick up and destroy untreated bait at the end of each day.

7. All 4-aminopyridien dust products must specify all bait preparation methods on the label under the section "Bait Preparation Directions." Bait preparation directions must include the following statement.

> Materials resembling human food must be altered in form by crushing, balling, or pelleting so that they are not readily recognizable as human food.

8. All 4-Aminopyridine products except ready-to-use baits intended for use on agricultural crops must specify all dilution methods and rates on the label under the section "Dilution Directions." Recommended dilution ratios must comply with the following.

> If the product is intended for the control of pigeons near nesting and roosting sites, no dilution ratio less than 1 part treated bait to 9 parts untreated bait may be recommended. A dilution ratio of 1 part treated bait to 29 parts untreated bait should be recommended for normal use (i.e., situations where other bird food is plentiful).
>
> If the product is intended for the control of sparrows, blackbirds, cowbirds, or crows in nesting or roosting structures, or for use in cattle feedlots, no dilution ratio less than 1 part treated bait to 9 parts untreated bait may be recommended.
>
> If the product is intended for the control of herring gulls at sanitary landfills or nesting and roosting sites, no dilution ratio less than 1 part treated bait to 10 parts untreated bait may be recommended.

9. Labels for 4-aminopyridine formulated products must comply with the requirements of 40 CFR 162.10 regarding label format, including placement of hazard warnings on the label, type size and color, etc.

To be covered under this Standard, all applicants for registration or re-registration of 4-aminopyridine ready-to-use bait and dust products must agree to submit or cite the following information on the physical/chemical composition of each proposed product. Listed after each data gap is the section in the Proposed Guidelines which describes that type of data and when it is required [43 FR, No. 132, 19696 of July 10, 1978, and 43 FR, No. 162,37336 of August 22, 1978].

Product Chemistry	Guideline Section
1. Color	163.61-8(c)(1)
2. Odor	163.61-8(c)(2)
3. Density	163.61-8(c)(3)
4. Storage Stability	163.61-8(c)(12)
5. Formation of Unintentional Ingredients	163.61-5
6. Percentages of Compounds Pesticide Products	163.61-6

All applicants for registration or re-registration of dust products must also agree to provide or cite an acute inhalation toxicity study (163.81-3) on a dust formulation. Two toxicology data requirements for 4-aminopyridine dust products are contingent upon label restrictions. Applicants for registration or re-registration of dust products must require applicators, by the label, to wear protective clothing including long sleeves, gloves, and respirators or they must agree to provide or cite the following studies:

Toxicology	
Teratogenicity	163.83-3
Mutagenicity	163.84-111, 2, 2, 4

Although certain 4-aminopyridine products are used to control birds at public facilities the Agency does not consider this use a public health use. The Agency is therefore waiving all efficacy requirements. In support of this waiver, when 4-aminopyridine products are used to control nuisance birds at public facilities, the user can readily see the results of the intended action of the pesticide, thereby eliminating the need for efficacy data.

Applicants are hereby advised that if the Agency does not receive commitments, within the specified time period, from manufacturing-use producers to fill data gaps identified for the manufacturing-use material, the registrations of the manufacturing-use products will be suspended. Formulators must then bear the burden of supplying the data if they want the manufacturing-use product to be available.

III. Product Chemistry

Product Chemistry Introduction

FIFRA 3(c)(2)(A) requires the Agency to establish guidelines for registering pesticides in the United States. Registrants are required to provide quantitative data on all added ingredients, active and inert, which are equal to or greater than 0.1% of the product by weight.

To establish the composition of products proposed for registration, the Agency requires data and information not only on the manufacturing and formulation processes, but also a discussion on the formation of manufacturing impurities and other product ingredients, intentional and unintentional. Further, to assure that the composition of the product as marketed will not vary from the composition evaluated at the time of registration, applicants are required to submit a statement certifying upper and lower composition limits for the added ingredients, or upper limits only for some unintentional ingredients. Subpart D suggests specific precision limits for ingredients based on the percentage of ingredient and the standard deviation of the analytic method.

In addition to the data on product composition, the Agency also requires data to establish the physical and chemical properties of both the pesticide active ingredient and its formulations. For example, data are needed concerning the identity and physical state of the active ingredient (e.g., melting and boiling point data, vapor pressure and solubility). Data are also required on the properties of the formulated product to establish labeling cautions (e.g., flammability, corrosivity or storage stability). The Agency uses these data to characterize each pesticide and to determine its environmental and health hazards.

The number in parenthesis next to the subheadings in the Product Chemistry Topical Discussions corresponds to the number of the section in the "Proposed Guidelines for Registering Pesticides in the United States" (43 FR 29696) which fully explains the minimum product chemistry data requirements.

Topical Discussions

Chemical Identity (163.61-3)

At present there is no acceptable common name for the bird repellent, 4-aminopyridine (8th Collective Index, 1973). Other chemical names for the compound include 4-pyridinamine (9th Collective Index, 1977), gamma-aminopyridine, and p-aminopyridine. "4-AP" is a commonly used abbreviation while "Avitrol", "Avitrol 200", "Compound 1861", and "Phillips 1861" are all trade names.

The Phillips Petroleum Company (no date, 00004019) speculated that 4-aminopyridine may also exist as a tautomeric form. However, Craig (1968, 05010341) presented an NMR spectral study which confirmed the amino structure. Baer (1943, 05006181) also confirmed the amino structure with U.V. absorption spectra data. Further characterization of 4-aminopyridine is noted in Appendix A, Chemical Data Sheet.

Manufacturing Process (163.61-4)

The Phillips Petroleum Company (Hyden, 1968, 00004148) submitted a description of the manufacturing process (Appendix B, Manufacturing Process, Confidential) in 1968. However, Phillips sold its 4-aminopyridine patents to Avitrol Corporation in 1972. The Agency has no information on the present commercial method of manufacture, which is conducted solely by Avitrol Corporation.

Two methods of preparing 4-aminopyridine have been discussed in the literature (Baer, 1943, 05006181). One method involves preparation from chelidonic acid, through 4-chlorpyridine-2,6-dicarboxylic acid. The second method involves preparation from pyridylpyridinium dichloride. It is uncertain whether either of these methods is currently used for commercial manufacture.

Formation of Unintentional Ingredients (163.61-5)

The Phillips Petroleum Company submitted information (Hyden, 1968, 00004148) on the contaminants of technical 4-aminopyridine but did not support the information with analytical data (Appendix B, Manufacturing Process, Confidential). In addition, no information is available on the contaminants which result from the current manufacturing process of 4-aminopyridine. Additional data on the formation of unintentional ingredients are therefore required.

Active Ingredient Limits in Pesticide Products (163.61-6)

The technical chemical prepared by Phillips Petroleum Company contained a minimum of 98% active ingredient (Hyden, 1968, 00004148). The confidential formula of the manufacturing use product is described in Appendix C, Formulation Processes, (Confidential). The formulas of nine products which appear on the labels are listed in Appendix B, Summary of Label Ingredient Statements. Certification of active and inert ingredients is not possible at this time due to a lack of information on the currently used manufacturing process for 4-Aminopyridine and the length of time which has passed since the original submission of formulas for registered products.

Product Analytical Methods and Data (163.61-7)

Phillips Petroleum (1962, 00003978, 1920, 00004020) submitted a method for analysis, by U.V. spectrophotometry, of grain seed impregnated with 0.1% - 3.0% 4-aminopyridine. This method was also used to assay their analytical standard. The EPA Manual (1976) describes a similar U.V. method for use on solid formulations. This method is adequate for the characterization of 4-aminopyridine. However, if impurities in the technical material were to be identified, analytical methods would also be needed for their assay.

Physical/Chemical Properties (163.61-8)

The following information (Phillips, 00004019, 00004112) applies to the technical compound except where otherwise noted.

Color: White (purified).
Off-white (technical grade).
No color reported for formulated products.

Odor: None (purified).
Slightly musty (technical).
No odor reported for formulated products.

Melting point: 158.9°C. (purified).
155-158°C. (technical).

Solubility: Water -- given as both 8% and 12% (free base).
-- 50% (HCl salt).
Acids -- soluble as the salts.
Acetone -- moderately to very soluble.
Methanol -- soluble.
Ether -- soluble.
Benzene -- soluble.
Soluble in most polar solvents.

These data are not adequate to assess the solubility of 4-aminopyridine. Solubilities must be expressed in quantitative terms, (g/100ml at 20°C, or ppm).

Stability: The free base is moderately stable to light. An aqueous solution of free base darkens slowly in light. The hydrochloride salt is light stable.

Octanol/Water Partition Coefficient: None reported.

Physical State: Crystalline solid (technical). The formulation intermediate is a granular (impregnated grain). The formulated products consist of granulars (impregnated grains), dusts and pelletized baits.

Density or Specific Gravity: Not reported.

Boiling Point: 273-274°C (760 mm Hg, technical).
Not applicable for formulated products.

Vapor Pressure: None reported (technical).

pH: Basic in reaction (technical).

Storage Stability: Four 0.25% 4-aminopyridine formulations of different impregnated grains were studied over a period of eight months at 82°F and 140-150°F after storage in four different kinds of containers. No 4-aminopyridine loss was reported. Actual use experiments were carried out for over a year on four 0.5% formulations with the same four impregnated grains. No loss of 4-aminopyridine was reported in the samples stored in completely protected feeders. There was a 40-50% loss of 4-aminopyridine in samples partly exposed to the weather.

Flammability: Not applicable.

Oxidizing or Reducing Action: Not reported.

Explosiveness: Not reported.

Miscibility: Not applicable.

Viscosity: Not applicable.

Corrosion Characteristics: Not reported.

DISCIPLINARY REVIEW
Product Chemistry Profile
Data Gaps
Required Labeling

Product Chemistry Profile

"Avitrol" is a well-known trade name for 4-aminopyridine. "4-AP" is a commonly used abbreviation. The technical compound is an off-white crystalline solid with a slightly musty odor. The hydrochloride salt is stable in light and soluble in water, acids, and most organic solvents. The technical compound is manufactured by the Avitrol Corporation in an integrated formulation system to produce a 0.3% impregnated grain formulation intermediate and end-use products.

The manufacturing-use product produced by Avitrol is reformulated into additional products by the Woodbury Chemical Company and the Huge' Company. All 4-aminopyridine is ultimately formulated into baits. Most of the end-use products are ready-to-use baits in which 4-aminopyridine is mixed with a variety of foodstuffs such as corn, wheat, sorghum, and mixed grains. The remaining end-use products are dust concentrates consisting of cornstarch and 25% or 50% 4-aminopyridine. These dusts are used to coat bread or french fries in order to make finished baits.

Data Gaps

Listed below are Product Chemistry data needed to obtain registration or reregistration for 4-aminopyridine products. Listed after each data gap is the number of the section in the Proposed Guidelines (July 10, 1978, 43 FR, No. 132,29696) which describes that type of data and when it is required.

For Technical	Guideline Section
1) Chemical Identity -- Complete identification of all impurities and reaction compounds (if any) in the technical chemical.	163.61-3
2) Manufacturing Process -- Complete description of the present-day manufacturing process, including type of process, equipment, quality control measures, etc.	163.61-4
3) Product Analytical Methods and Data -- Methods of analysis for identifiable impurities (if any) in the technical compound.	163.61-7
4) Solubility -- in quantitative terms	163.61-8(c)(4)
5) Octanol/Water Partition Coefficient	163.61-8(c)(6)
6) pH -- aqueous solution	163.61-8(c)(11)
For Manufacturing-use Product:	
7) Density	163.61-8(c)(8)
For Formulations (Ready-to-Use Baits and Dusts):	
8) Color	163.61-8(c)(1)
9) Odor	163.61-8(c)(2)
10) Density	163.61-8(c)(8)
11) Storage Stability (dust and pellets only)	163.61-8(c)(12)
12) Formulation of Unintentional Ingredients -- Theoretical discussion of the formation of each substance, aside from the active ingredient and intentionally added inert ingredients, that might reasonably be identifiable as being present in the pesticide product.	163.61-5
13) Percentages of Components in Pesticide Products -- Declaration/certification of limits for all active and inert ingredients.	163.61-6

Required Labeling

The ingredient statement will list the active ingredient as:

4-aminopyridine ....________%

Additional labeling may be required following review of physical/chemical properties data provided at the time of registration or reregistration.

Product Chemistry Bibliography

05006181 Baer, J.E. (1948) Alkyl Polysulfide and 4-aminopyridine and Related Compounds [Doctoral Dissertation]. Philadelphia, Pa: University of Pennsylvania. (Twenty-one unpaged figures)

05010341 Craig, J.C., Jr.; Pearson, D.E. (1968) NMR proof of the structure of 4-aminoquinolines and pyridines. Journal of Heterocyclic Chemistry 5(5):631-637.

00004148 Hyden, S. (1968) Bird Management Process: LDG-123-68P. (Unpublished study received Jul 17, 1968 under unknown admin. no.; prepared by Nepera Chemical Co., submitted by Phillips Petroleum Co., Bartlesville, Okla.; CDL:103068-A)

00004112 Phillips Petroleum Company (no date) Technical Data Sheet: Phillips Avitrol 200 (1861). (Unpublished study received 1968 under unknown admin. no.; CDL:221959-B)

00004019 Phillips Petroleum Company (no date) [Identity, Physical and Chemical Properties, and Formulations of Avitrol]. (Unpublished study received Jul 13, 1970 under 1F1013; CDL:093322-D)

00003978 Phillips Petroleum Company (1962) Determination of 4-aminopyridine in Grain Seed: Ultraviolet Spectrophotometric Method. Method PK-62R dated Jan 12, 1962. (Unpublished study received Aug 13, 1963 under 224-EX-1; CDL:122741-A)

00004020 Phillips Petroleum Company (1970) Determination of 4-aminopyridine in Grain Seed Ultraviolet Spectrophotometric Method. (Unpublished study including letter dated Jun 26, 1970 from A.M. Schnitzer to U.S. Food and Drug Administration, Pesticides Branch, Reference Standards Section, received July 13, 1970 under 1F1013; CDL:093322-F)

Standard References

Chemical Abstracts Service (1973) Chemical Abstracts 8th collective index, Vols 66-75 (1967-1971), American Chemical Society.

Chemical Abstracts Service (1977) Chemical Abstracts 9th collective index, Vols 76-85 (1972-1976), American Chemical Society.

U.S. Environmental Protection Agency (1976) Manual of chemical methods for pesticides and devices. Washington, D.C.

U.S. Environmental Protection Agency (1978) Proposed Guidelines for the registering of pesticides in the United States. Federal Register, 43 (132) 29696 - (July 10, 1978).

IV. Environmental Fate

Use Profile

4-aminopyridine is the active ingredient in several federally registered pesticide products. It is currently registered for the control of nuisance and depredatory birds such as blackbirds, crows, cowbirds, starlings, gulls, and common grackles. Application sites include field corn, sweet corn, and sunflower fields, and urban and agricultural premises. Between 330 and 350 pounds of 4-aminopyridine are produced yearly (Avitrol, 1980, personal communication). Approximately 104 pounds are used on agricultural crops and approximately 240 pounds are used on agricultural premises and in urban areas.

All 4-aminopyridine is ultimately formulated into baits. The baits are placed in areas where large numbers of nuisance or depredatory birds congregate. The baits work by causing the birds that eat them to utter distress calls which serve to scare the rest of the flock away. Birds that eat the treated bait usually die.

Registered 4-aminopyridine products which are used on crops are 3% pretreated baits. The baits are mixed prior to application at a ratio of one treated particle to 99 untreated particles. The mixture actually applied therefore contains 0.03% 4-aminopyridine. Current label directions call for the application of one pound of bait per total acre applied to one-third of an acre at a time, resulting in a rate of 3 lbs/acre on the treated portion. When applied to sunflowers, only areas of 15 or more acres are treated. Succeeding applications are made on previously untreated areas so that the material is eventually spread over the entire area. Labels direct product users to make applications to corn fields "when bird damage becomes apparent" and to make applications to sunflower fields "when bird damage reaches 200 freshly damaged heads, or when at least 200 feeding target birds are observed in a field". Treatments are made a maximum of four times per season in corn fields and a maximum of five times per season in sunflowers.

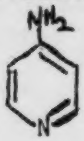
Other registered formulations include 50% and 25% 4-aminopyridine dusts and pretreated bait formulations containing from 0.02% to 1% active ingredient. These formulations are used for the control of nuisance birds at urban nesting and roosting sites, cattle feedlots and sanitary landfills. Current use directions call for scattered spot placements of untreated bait followed by placements of treated bait after feeding patterns at the bait sites have been established. Labels for 4-aminopyridine products used at urban facilities direct applicators to place the baits at the appropriate feeding sites, in high locations on buildings and ledges. Labels for 4-aminopyridine products used at cattle feedlots direct applicators to place the bait in elevated feeders, out of reach of farm animals.

Products containing 4-aminopyridine are restricted use pesticides registered for sale to and use only by certified applicators or persons under their direct supervision. These products are not for sale to the general public.

Topical Discussions

Numbers in parentheses next to topical discussion subheadings correspond to the number of the section in the proposed Guidelines (U.S. Environmental Protection Agency, 1978) which explains the minimum data requirement of that topic.

AVITROL 200^{R}



4-Aminopyridine

Physico-Chemical Transformation (163.62-7)

(A) Hydrolysis 163.62-7(b)

Hydrolysis data are required in most cases, to support the registration of manufacturing-use products, regardless of the intended end uses of products formulated from the manufacturing-use product. These data are not required for 4-aminopyridine, however, because the chemical is a minor use pesticide with a total yearly production of less than 350 pounds. Should yearly production of 4-aminopyridine reach 25,000 pounds, hydrolysis data on the technical chemical will be required.

(B) Photolysis 163.62-7(c)

Photodegradation studies in water are required, in most cases, to support the registration of formulated products intended for terrestrial uses. Studies in soil are required in most cases to support the registration of formulated products intended for crop uses. These studies are not required for 4-aminopyridine, however, because residues of 4-aminopyridine are not expected to reach significant levels in soil or water as a result of application of 4-amiminopyridine formulated products (Metabolism-Soil and Exposure Profile below).

Metabolism 163.62-8

Data on metabolism are required to determine the nature of pesticide residues and their availability to rotational crops, to help in the assessment of potential disposal and reentry hazards, and to assist in predicting the persistance and extent of residue accumulation.

(A) Soil 163.62-8(b,c)1

Aerobic metabolism studies are required to support the registration of all formulated 4-aminopyridine products intended for terrestrial uses. Anaerobic soil metabolism studies are required to support the registration of all formulated products intended for field and vegetable crop uses.

Of three soil metabolism studies submitted, two were considered valid. Starr and Cunningham (1975, 05003185) investigated the degradation of 4-aminopyridine, as measured by $^{14}CO_2$ evolution, in various soil types (loamy sand, sandy loam, loam, and sandy clay loam) under aerobic and flooded conditions. In alkaline soil under aerobic conditions, 4-aminopyridine, when applied at 10 ppm, exhibited half-lives ranging from 3 months in loamy sand to 32 months in sandy clay loam. Extensive degradation to CO_2 occurred after a lag period of over 7 days. However, under flooded conditions, very little (<0.5%) [^{14}C] 4-aminopyridine degradation was detected within the same period.

Rates of metabolism of [^{14}C] 4-aminopyridine in soil under aerobic conditions increased with increasing organic matter. When metabolized in two slightly acidic (pH 5.6-5.8) loam soils containing 16% clay, [^{14}C] 4-aminopyridine was degraded to $^{14}CO_2$ faster (t 1/2 = 8 months) in the soil with 5.0% of organic matter than it was in the soil with 2.9% organic matter (t 1/2 = 22 months).

Rates of metabolism also increased with increasing soil pH. The amount of $^{14}CO_2$ recovered over a 3-month period was minute (0.35%) for a highly acidic loam (pH 4.1), but was much greater (4.88%) for an alkaline sandy clay loam with similar levels of organic matter and clay. In these tests, degradation of 4-aminopyridine was measured only by $^{14}CO_2$ recovery. No attempt was made to identify intermediate degradation products.

Betts et al. (1976, 05003407) investigated the degradation of [2-^{14}C] 4-aminopyridine (10 ppm) in sandy loam, fine loamy sand, and clay soils under aerobic and flooded conditions. Under aerobic conditions, the half-lives of 4-aminopyridine ranged from 8 months in the clay soil to 32 months in the sandy loam soil. A lag period of 20 days occurred before extensive degradation to CO_2 was observed. Under flooded conditions, the half-lives of 4-aminopyridine ranged from 8 months in the clay soil to approximately 10 months in the sandy loam soil. These half-lives are based on $^{14}CO_2$ evolution. No intermediate degradation products were detected in extracts from soils under either aerobic or flooded conditions.

The studies by Betts et. al (1976, 05003407) and Starr and Cunningham (1975, 05003185) show that 4-aminopyridine residues would be fairly persistent in soil, but they do not fully characterize 4-aminopyridine soil metabolism. No additional studies are needed, however, because of the following:

1) Only a small amount (approximately 104 lbs) of 4-aminopyridine is used on crops yearly. Accumulation in soil, based on the maximum allowable use, together with available data, should not exceed 1.6 mg per square meter.

2) When applied at cattle feedlots, 4-aminopyridine treated baits will be placed off the ground, out of reach of cattle. Therefore, very little direct-soil contact is expected.

3) Similarly, no significant direct-soil contact is expected from urban uses.

4) Since the total amount of 4-aminopyridine applied yearly in all landfills is less than 10 lbs, residue levels in soil resulting from this use are expected to be very small. In addition, at the site of application, any residues which might accumulate would not be expected to be available to rotational crops.

In summary, the lack of significant 4-aminopyridine residues available to rotational crops eliminates the need for fully assessing 4-aminopyridine soil metabolism.

(B) Microbiological Studies 163.62-8(f)

Data on the effects of microbes on pesticide degradation and the effects of pesticides on microbes are required in most cases to support the registration of formulated products intended for terrestrial use.

(1) Microbiological-Effects of Microbes on Pesticides 163.2-8(f)(2)

One study (Betts, et al, 1976, 05003407) on the ability of soil microorganisms to metabolize 4-aminopyridine was reviewed. In the study, pure cultures of *Aspergillus niger*, *Pseudomonas fluorescens*, *Enterobacter aerogenes*, *Streptomyces griseus*, and *Agrobacterium tumefaciens* failed to metabolize 4-aminopyrdine when incubated in the presence of the compound at concentrations of 10 and 100 ug/ml for 5-6 days. Microbiological rates in the pure cultures were not retarded by the pesticide. These data cannot be considered conclusive however, because too few species of microorganisms were examined and culture conditions were not varied enough.

(2) Microbiological - Effects of Pesticides on Microbes 163.62-8(f)(3)

Preliminary data on the effects of 4-Aminopyridine on microbes were reviewed. The study by Betts et. al. (1976, 05003407) indicated that the growth of *A. niger*, *P. fluorescens*, *E. aerogenes*, *S. griseus*. and *A. tumefaciens* was not retarded when incubated in the presence of 4-aminopyridine at concentrations of 10 or 100 ug/ml for 5-6 days. These data cannot be considered conclusive, however, because too few species of microorganisms were examined.

Although the data discussed above are inconclusive, no additional microbiological studies are required because 4-aminopyridine soil residues potentially available to rotational crops are expected to be insignificant (Metabolism-Soil above)

(C) Activated Sludge 163.62-8(g)

A laboratory study of the effects of pesticides on the wastewater treatment process is required to support the registration of all manufacturing-use products and all formulated products that are indirectly discharged into wastewater treatment systems or are used as treatments in wastewater treatment systems.

4-aminopyridine formulated products will neither be indirectly discharged into, nor used as treatments for wastewater treatment systems. Therefore, data on the effects of such products on the wastewater treatment systems are not required. Neither are activated sludge data required for 4-aminopyridine manufacturing-use products, since total yearly production of the chemical is small (see discussion on hydrolysis data above). Should yearly production of 4-aminopyridine reach 25,000 pounds, activated sludge data on the technical chemical would be required to support 4-aminopyridine manufacturing-use products.

Mobility 163.62-9

Data on mobility are required to determine pesticide residue movement in the environment.

(A) Leaching 163.62-9(b)

Leaching data are required to support registration of formulated products intended for terrestrial noncrop and field/vegetable crop uses.

Two leaching studies were reviewed. In a study by Starr and Cunningham (1975, 05003185), seven different types of alkaline and acidic soils (Table 1) were fortified with [^{14}C] 4-aminopyridine at 10 ppm. Over a 20-day period, approximately 7 inches of water were applied to columns containing the fortified soil. At the end of the leaching period, detectable radioactivity was found in the leachate from all of the alkaline soils, but in the leachate from only one of the acidic soils. Total detectable radioactivity in the leachate never exceeded 0.2% of the initial ^{14}C application. Analysis of the soil columns after the leaching treatment showed that for all soils more than 95% of the recoverable ^{14}C was in the upper 1-inch of soil.

In a second study (Starr and Cunningham, 1979, 00004001) alkaline soils including loamy sand, sandy clay loam, and loam were packed into columns, with corn seedling planted in each column. The soils were fortified with [^{14}C] 4-aminopyridine at 10 ppm and leached with a total of 5.8 inches of water over a 7-day period. Less than 0.03% of the applied radioactivity leached through the soils during the 7-day treatment period. Analysis of radioactiviry in all of the soils at the conclusion of the leachate experiments showed that greater than 97% of the total radioactivity found was in the top 1 inch of the soil. These studies indicate that 4-aminopyridine is relatively

Table 1. Leaching of [^{14}C]4-Aminopyridine (10 ppm) from soil columns after elution with 7 inches of water over 20 days.[a]

Soil	Soil type	pH (paste)	Organic matter (%)	Sand (%)	Silt (%)	Clay (%)	Radioactivity recovered from leachate (%)	Radioactivity remaining in upper inch of soil column[b] (%)
				Alkaline soils				
A	Loamy sand	7.8	2.9	77	16	7	0.18	95
B	Sandy clay loam	7.7	4.0	61	19	20	0.02	99
C	Sandy clay loam	7.6	1.9	47	27	26	0.09	98
D	Loam	7.6	2.5	59	30	11	0.01	--c
				Acidic soils				
E	Loam	5.8	2.9	46	38	16	<0.01	>99
F	Loam	5.6	5.0	50	34	16	--	>99
G	Sandy loam	5.6	4.0	53	33	14	--	>99
H	Loam	4.1	1.4	31	44	25	--	>99

[a] Adapted from Starr and Cunningham (MRID 05003185; MRID 00004001).

[b] Percent of total recovered from soil columns.

[c] Not measured.

immobile in soils.

Because the experimental soils were leached with less than half the amount of water recommended by the Proposed Guidelines, these studies would not be considered adequate to assess the leaching potential of a major crop use chemical. However, since the total amount of 4-aminopyridine applied yearly is quite small, residue levels in soil are expected to be insignificant (See 2A above). Therefore, no additional data on the leaching potential of 4-aminopyridine are required.

(B) Adsorption/Desorption 163.62-9(d)

A laboratory study using radioisotopic or nonradioisotopic analytical techniques is required, in most cases, to support the registration of products intended for terrestrial uses. These data are not required for 4-aminopyridine because accumulation of 4-aminopyridine in soil is expected to be insignificant.

(C) Terrestrial Field Dissipation 163.62-10(b)

A field dissipation study under actual use conditions is required, in most cases to support the registration of formulated products intended for terrestrial uses. This study is not required for 4-aminopyridine because accumulation of 4-aminopyridine in soil is expected to be insignificant.

Accumulation 163.62-11

Data on accumulation are required to determine accumulation in food webs.

(A) Rotational Crops 163.62-11(b)

Rotational crop studies are required, in most cases, to support the registration of formulated products intended for field/vegetable uses. 4-Aminopyridine residue levels in soil available to rotational crops are expected to be insignificant (approximately 1.6 mg/m^2). Consequently, no significant residues of 4-aminopyridine are expected to occur in rotational crops, thus eliminating the need for 4-aminopyridine rotational crop studies.

(B) Fish 163.62-11(d)

This laboratory study employing radioisotopic or nonradioisotopic analytical techniques is required in most cases to support the registration of formulated products intended for terrestrial and field/vegetable crop uses. A fish accumulation study is not required for 4-aminopyridine, however, because residues in aquatic systems are not expected to result from current uses of the formulated products.

DISCIPLINARY REVIEW
Environmental Fate Profile
Exposure Profile

Environmental Fate Profile

Residue levels of 4-aminopyridine in soil resulting from terrestrial application of 4AP formulated products are expected to be very low. The following discussion characterizes the fate of 4-aminopyridine in soil were it to accumulate in soil.

4-aminopyridine is fairly persistent in soil. Under aerobic conditions, 4-aminopyridine exhibited half-lives ranging from 3 months to 32 months in a variety of soils. A lag period of 7-20 days was required before extensive degradation to carbon dioxide occurred. Under flooded conditions half-lives ranged from 8 months in clay soil to 10 months in sandy loam soil.

The rate of aerobic soil metabolism of 4-aminopyridine increases with increasing organic matter. Of two slightly acidic loam soils studied, the soil with 5% organic matter degraded the compound to carbon dioxide almost three times faster than the soil with 2.9% organic matter. Soil pH also influences 4-aminopyridine metabolism. Recovered carbon dioxide was almost negligible for a highly acidic loam (pH 4.1) but was somewhat greater for alkaline sandy clay loam with similar levels of organic matter and clay. Degradation of 4-aminopyridine was measured only by carbon dioxide recovery; no attempt was made to identify intermediate degradation products.

The rate of microbial degradation of 4-aminopyridine appears to be slow. Several common soil microorganisms, *Aspergillus niger*, *Pseudomonas fluorescens*, *Streptomyces griseus*, and *Agrobacterium tumefaciens*, were unable to degrade the chemical within 120 hours. 4-aminopyridine appears to have no effect on microbial growth. Microbial growth rates in pure cultures were not retarded by the pesticide at concentrations of 10 and 100 micrograms/ml. These results are inconclusive however, and the ability of microorganisms to degrade 4-aminopyridine as well as the effect of the pesticide on microbes remains uncertain. Available data on the mobility of 4-aminopyridine suggest that the compound does not leach significantly in soil. When soil columns containing acidic loam or sandy loam soils (pH 4.1-5.8) were eluted with water over a 20-day period, greater than 99% of the applied compound remained in the top inch of soil. Low quantities of 4-aminopyridine were found in the leachate of one of the acidic soils (less than 0.01% of the initial application) and in all of the alkaline soils (0.09-0.18%).

Because 4-aminopyridine strongly adsorbs to the soil, it will remain near the soil surface, where maximim microbial degradation is likely to occur. However, the rate of microbial degradation is, at best, rather slow. Therefore, any 4-aminopyridine residues present in soil will probably persist for a considerable period. Because 4-aminopyridine appears to be tightly held to soil under most or all circumstances examined, migration of the chemical from the site of application will be minimal.

Exposure Profile

For persons involved in the dilution, mixing, and application of 4-aminopyridine products, there is little chance of oral exposure except through accidental ingestion. 4-aminopyridine is registered for use on food crops but 4-aminopyridine residue levels in the crops should be insignificant, so there is very little possibility of dietary exposure to 4-aminopyridine for the general public.

Because 4-aminopyridine ready-to-use bait formulations consist of grains, such as corn and wheat, impregnated with 4-aminopyridine during the manufacturing process, no occular or inhalation exposure to these formulations should occur. There is a chance of dermal exposure, but applicators would be exposed to only very small amounts of active ingredient. Applicators who handle dust formulations may receive dermal and inhalational exposure because the bait preparation process involves manual mixing of the active ingredient with bait material. The use of protective clothing, including long sleeves, gloves, and respirators during the handling of dust formulations, will essentially eliminate all but accidental dermal, occular, and inhalation exposure to dust products.

Due to the nature of 4-aminopyridine formulations, the potential for contamination of nontarget sites by drift is negligible. The extremely low rates at which 4-aminopyridine is applied to crops and to sanitary landfills, and the lack of direct soil contact with formulations applied to cattle feedlots and urban areas should prevent significant 4-aminopyridine accumulation in soil. 4-aminopyridine is not expected to be present in ground water or surface water as a result of terrestrial application of 4-aminopyridine formulated products.

The potential for exposure to 4-aminopyridine formulations is greatest for nontarget wildlife, specifically, grain-feeding birds. The greatest risk to migratory birds will occur during the fall migration period when finches and other small seed-feeding birds may ingest lethal doses of the pretreated baits applied to corn and sunflower fields. Observations (McCann, 1980, #0015005) indicate, however, that in areas where 4-aminopyridine is most often used (the midwest) most migratory birds will pass through after the corn is harvested. In addition, field reports (Besser and Cummings, 1975 #0000479) indicate that in a year of normal maturation of sunflowers baiting will be completed before most finches, sparrows and other birds migrate.

Environmental Fate Bibliography

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05003185 Starr, R.I.; Cunningham, D.J. (1975) Leaching and Degradation of 4-aminopyridine ^{14}C in Several Soil Systems. Archives of Environmental Contamination and Toxicology 3(1):72-83.

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V. Ecological Effects

Ecological Effects Topical Discussions

Effects on Avian Species (163.71-1,2,4,5)

Effects on avian species can be measured by acute, subacute, reproduction, and field studies. The studies required for a particular chemical depend upon the use pattern of the chemical and the results of particular tests.

Acute Effects: The minimum data required for establishing the acute toxicity of 4-aminopyridine are results from avian single-dose oral LD_{50} studies using technical 4-aminopyridine. Test species should be either wild waterfowl (preferably the mallard duck) or upland game birds (preferably the bobwhite quail or the ring-necked pheasant).

Two valid studies on the acute effects of 4-aminopyridine on a variety of species were available for review. Table 1 summarizes the results of these studies.

Table 1. Studies on the Acute Toxicity of Technical 4-Aminopyridine to Avian Species

Author	Species	Test Substance	Results
Schafer, et al, 1975 (05003186)	Blackbilled magpie	Technical	Oral LD_{50} = 2.4 mg/kg
	Yellowbilled magpie	Technical	Oral LD_{50} = 2.4 mg/kg
	Sparrow hawks	Technical	Oral LD_{50} = 5.6 mg/kg (4.2 - 7.5 mg/kg)
Schafer et al, 1973 (05003191)	Quelea	Technical	Oral LD_{50} = 5.6 mg/kg
	House Sparrow	Technical	Oral LD_{50} = 7.5 mg/kg
	Red-winged blackbird	Technical	Oral LD_{50} = 2.4 mg/kg

While neither of these studies alone fulfills the Proposed Guideline (U.S. Environmental Protection Agency, 1978) requirement for the avian single dose oral LD_{50}, the studies taken together provide sufficient information to characterize 4-aminopyridine as highly toxic to avian species. Consequently, no further acute avian toxicity studies are required.

Subacute Effects: The minimum data required for establishing the subacute toxicity of 4-aminopyridine in birds are as follows: Avian dietary LC_{50} studies for one wild waterfowl species (preferably the mallard duck) and one upland gamebirds species (preferably the bobwhite quail or the ring-necked pheasant).

Three valid studies were available for review on this topic. Table 2 summarizes the available subacute data.

Table 2. Studies on the Subacute Toxicity of Technical 4-aminopyridine to Avian Species

Author	Species	Test Substance	Results
Schafer, et al, 1975 (05003186)	Coturnix Quail	Technical	LC_{50} = 447 ppm (289 - 714 ppm)
	Mourning Dove	Technical	LC_{50} = 316 ppm (100 - 1000 ppm)
Schafer & Marking, 1974 (00004083)	Coturnix Quail	Technical	LC_{50} = 479 ppm (354 - 645 ppm)
	Coturnix Quail	Technical	LC_{50} > 316 ppm
Fink & Reno 1976 (GS-0015-004)	Mallard Duck	Technical	LC_{50} = 772 ppm (547.3 - 952.5 ppm)

Based on this information, 4-aminopyridine can be characterized as moderately toxic to upland game birds and waterfowl.

Avian Reproduction: Avian reproduction toxicity studies on technical 4-aminopyridine are necessary if the pesticide is persistent in the environment, if it is stored or accuumulated in plant or animal tissues, if its use is such that nontarget birds may be exposed repeatedly or continuously to sublethal doses (especially before breeding season), or if available test information indicates that avian reproduction may be adversely affected by use of the pesticide.

Schafer et. al. (1975, 05003186) conducted an avian reproduction study on coturnix quail. The effects of chronic and single-dose exposures were studied. In the chronic feeding test, 4-aminopyridine was incorporated into the diet at concentrations of 31.6, 100, and 316 ppm. No significant differences in egg production or hatchability were found through the F1 generation. Further generations were not studied. In the single exposure study, a dose of 5.66 mg/kg 4-aminopyridine did not affect egg production or hatchability.

The preferred test species was not used in this study nor was egg shell thickness measured. In addition, the study was carried out for only four weeks instead of the preferred ten week period, only three concentrations were administered instead of the preferred four, and fewer birds than the preferred number were tested. Despite these deficiencies, the study demonstrated for coturnix quail that no adverse reproductive effects will result from a chronic dose of 316 ppm or a single dose of 5.62 mg/kg. In view of these results, the high acute avian toxicity of the compound, and the method of use of the compound (distribution of discrete bait granules), it is unlikely that birds would consume sublethal doses that would adversely affect reproduction. No additional avian reproduction studies are required.

Special Studies: Several special toxicity studies on both technical 4-aminopyridine and formulated products were available for review. Schafer et al. (1970, 00003998) found no observable effects at 31.6 and 100 ppm dietary levels after 30 days of feeding 4-aminopyridine to mourning doves. However, at the next level, 316 ppm, 50% mortality occurred. This study further confirms previous LC_{50} studies.

Schafer et al. (1973, 05003191) also conducted a study to determine the acute dermal LD_{50} for quelea and house sparrow. The value determined was greater than 100 mg/kg for both birds. This LD_{50} value indicates that 4-aminopyridine is only slightly toxic when applied dermally to birds.

Several avian feeding studies on the formulated product were available for review for 4-aminopyridine. Table 3 summarizes these results.

Table 3. Avian Feeding Studies on the Formulated Product

Author	Species	Results
Schafer & Lockyer no date, (00003999)	Mourning Doves	Both 2% and 3% baits were lethal after a 7-day feeding period. The baits were diluted at a ratio of 1:99.
Besser, 1968 (00004101)	Bobwhite Quail	No toxic effects were seen at 1:99 dilution ratio of the 3% active ingredient bait.
Schafer & Marking, 1974 (00004083)	Bobwhite Quail	All birds died at the 1:29 dilution ratio of the 3% active ingredient bait.
Schafer & Marking, 1974 (00004083)	Starlings	LC_{50} > 1.78 mg/kg/day

Schafer et al. (1974, 00003965) designed a secondary poisoning study which included blackbilled magpies, sharp-shinned hawks, red-tailed hawks, and American Kestrels. The birds exhibited no symptoms of intoxication, nor any gross pathological changes when fed birds killed with 3% baits. Secondary poisoning toxicity appears to be nonexistent for 3% (per treated granule) products. However, no data were available to determine the potential for secondary poisoning of avian predators from 25% or 50% dusts or from pretreated baits containing greater than 3% (per treated granule) 4-aminopyridine.

Besser and Cumming (1975, 0004079) conducted a field study in which searches for dead nontarget and target birds were made in North Dakota, Minnesota and South Dakota sunflower fields treated with 4-aminopyridine. In one part of the study, two relatively small areas (35.65 and 51.5A) were searched intensively, along with nearby shelter belts and pastures. During the search, 258 target and 42 nontarget birds were found dead. Grackles and redwings accounted for 231 (90%) of the dead target birds. Slate-colored juncos and Harris sparrows accounted for 26 (62%) of the dead nontarget birds.

The second part of the study involved an 18,000 acre area of which only 128 acres were searched. The search in this area disclosed a total of 32 dead birds: 29 target birds (all black birds), 2 nontarget birds (1 mourning dove and 1 song sparrow) and 1 unidentified bird. The authors reported that the ratio of target to nontarget species found closely agreed with findings of searches made in heavily damaged fields during the previous six years. (Besser and Cummings, 1975, (00004079)).

Effects on Aquatic Organisms (163.72-1,2,3,4,5,6)

Effects on aquatic organisms are measured by a variety of tests, including fish acute LC_{50}'s, acute toxicity tests on aquatic invertebrates and estuarine and marine organisms, and embryolarvae and life cycle studies. The types of tests required depend on the pesticide use pattern and the results of previous tests.

Fish Acute LC_{50}: The minimum data required, in most cases, for establishing the acute toxicity of 4-aminopyridine to fish are results from 96-hour exposure studies on one cold water species (preferably rainbow trout) and one warm water species (preferably bluegill), using technical 4-aminopyridine. Valid data on two species were available for review on this topic. The acceptable acute toxicity data are summarized in Table 4.

Table 4. Studies on the Acute Toxicity of Technical 4-aminopyridine to Freshwater Fish

Author	Warmwater Fish Species	Water Temp	Hardness	Results
Schafer & Marking, 1974 (00004083)	Channel Catfish	12°C	very soft	LC_{50}=4ppm (3.2-5.0ppm)
			soft	LC_{50}=4ppm (3.4-4.7ppm)
			hard	LC_{50}=4ppm (3.6-4.5ppm)
			very hard	LC_{50}=2.43 (2.2-2.8ppm)
		17°C	soft	LC_{50}=4.36ppm (3.9-4.8ppm)
		22°C	soft	LC_{50}=5.80ppm (5.2-6.4ppm)
Schafer & Marking, 1974 (00004083)	Bluegill	12°C	very soft	LC_{50}=3.40ppm (3.0-3.9ppm)
			soft	LC_{50}=4.41ppm (3.8-5.1ppm)
			hard	LC_{50}=2.82ppm (2.3-3.5ppm)
			very hard	LC_{50}=3.20ppm (2.7-3.8ppm)
		17°C	soft	LC_{50}=5.60ppm (4.80-6.5ppm)
		22°C	soft	LC_{50}=7.56ppm (6.3-9.1ppm)

Based on these results, 4-aminopyridine can be characterized as moderately toxic to warm water fish. Although no data on cold water fish were submitted, none are required for 4-aminopyridine formulated products because 4-aminopyridine residues should not occur in water as a result of application of the formulated products. In addition, because 4-aminopyridine is a minor use pesticide that has a total yearly production of less than 350 pounds, an acute toxicity study on cold water fish is not required for manufacturing-use 4-aminopyridine. In further support of this data waiver, a valid study was available on warm water fish species which provides some basis for determining the toxicity of 4-aminopyridine to fish. However, should yearly production of 4-aminopyridine reach 25,000 pounds, an LC_{50} for cold water fish will be required to support the registration of manufacturing-use 4-aminopyridine products.

Effects on Mammals

Special mammalian toxicity studies on technical 4-aminopyridine can be required under circumstances described in Sec. 163.71(d) of the Proposed Guidelines.

One valid study was available on this topic. Schafer (1974, 00003965) designed a secondary poisoning study in which a beagle-coyote hybrid, one beagle, and ten white laboratory rats were fed redwing blackbirds contaminated with 4-aminopyridine. The largest dose consumed by a rat in these experiments was 1 redwing blackbird which had been dosed at a rate equal to 300 mg/kg. The 300 mg/kg dose fed to the blackbird was equal to 67 mg/kg or 3.4 LD_{50} doses for the rat. The highest dose given to a dog was 10 redwings which had been dosed at a rate of 150 mg/kg. The dose given to the 10 redwings was equal to 8.22 mg/kg, twice the dog's LD_{50} dose. Neither the rats nor the dogs exhibited symptoms of intoxication or any gross pathological changes. This study indicates that the hazard to mammals from secondary poisoning is minimal.

Phytotoxicity

Two valid studies (Starr and Cunningham, 00004037; 1974, 05003440) on phytotoxicity were available for review. Data from the studies showed that corn germination was unaffected at 1 ppm (the highest level tested), and that both corn and sorghum growth were unaffected in a 100 ppm solution of technical 4-aminopyridine.

Acute Toxicity to Aquatic Invertebrates (163.72-2)

A determination of the EC_{50} or LC_{50} for an aquatic invertebrate is required, in most cases, to support the registration of all manufacturing-use products. These data are not currently required for 4-aminopyridine, however, because it is a minor use pesticide (refer to above discussion on Fish Acute LC_{50}).

DISCIPLINARY REVIEW
Ecological Effects Profile
Ecological Effects Hazard Assessment
Data Gaps
Required Labeling

Ecological Effects Profile

Acute oral LD_{50} and dietary LC_{50} data indicate that 4-aminopyridine is acutely toxic to several avian species including magpies, sparrowhawks, house sparrows, and red-winged black birds. It is moderately toxic to upland gamebirds and wild waterfowl. Results of an avian reproduction study suggest that adverse avian reproductive effects resulting from ingestion of sublethal doses are unlikely.

LC_{50} values for two warm water fish species indicate that 4-aminopyridine is moderately toxic to these species. Cold water species were not tested.

Available data on the effects of feeding birds contaminated with 4-aminopyridine to avian predators and mammals suggests that secondary poisoning of mammals is unlikely to result from use of this compound and secondary poisoning of avian species is unlikely to result from use of 3% or less pretreated baits. The only phytotoxicity data available indicate that 4-aminopyridine is not significantly toxic to corn or sorghum. One ppm does not affect seed germination in corn and a 100 ppm solution does not affect the growth of corn or sorghum.

Ecological Effects Hazard Assessment

Although 4-aminopyridine is acutely toxic to some bird species and at least moderately toxic to others, the hazard to nontarget migratory birds from 3.0% (per treated granule) 4-aminopyridine ready-to-use baits applied to agricultural crops is slight. Most nontarget migratory birds are expected to pass through corn areas after the crop is harvested. In addition, in a year of normal maturation of sunflowers, all sunflower baiting will have been completed prior to the period during which most nontarget birds migrate. Migratory nontarget birds may still be killed occasionally however, due to variations in the time of migration and in the time of crop harvest.

Mourning doves and bobwhite quails, which are nonmigratory species, may potentially be exposed after each application of ready-to-use baits to corn and sunflower fields. However, when the 3% (per treated granule) baits are applied to fields at a ratio of one treated granule to 99 untreated granules, the likelihood of a nontarget bird picking up more than 1 treated granule is small. At the 1:99 dilution ratio and the current application rate, only about 200 treated granules per acre are applied to corn and sunflower fields. One 3.0% 4-aminopyridine granule is not expected to be lethal to either doves or quails. In addition, 28-40 day LC_{50} dietary studies show that 4-aminopyridine has no cummulative toxic effect; several sublethal doses have no greater effect than a single sublethal dose. Therefore, it appears that in the field, the 1:99 dilution ratio reduces the hazard to doves and quails although sublethal doses may intoxicate these and other birds, leaving them more vulnerable to predation. Available data indicate, however, that if a 1:29 dilution ratio were used in the field, high dove and quail mortality could result (see Table 3).

The hazard to nontarget birds from 4-aminopyridine pretreated bait and dust products applied to cattle feedlots, sanitary landfills, and urban buildings should be slight, since these formulations are restricted to use only in areas where target birds are feeding. Secondary poisoning of mammals is not expected to occur as a result of application of any 4-aminopyridine product. Neither is secondary poisoning of avian predators expected to occur as a result of application of 3.0% or less (per treated granule) 4-aminopyridine ready-to-use baits. Due to a lack of data, however, the potential for secondary poisoning of avian predators from ready-to-use baits containing greater than 3.0% 4-aminopyridine (per treated granule) and from dust products, cannot be determined. Adverse avian reproductive effects resulting from sublethal doses of 4-aminopyridine are unlikely.

4-aminopyridine residues in water, resulting from terrestrial application of 4-AP formulated products, are expected to be insignificant. But assuming the "worst possible case" (i.e., direct application to water which is prohibited by label restrictions), at the current maximum application rate of .0144 oz. per acre the amount expected in an acre of water six inches deep is well below the LC_{50} of 2.43 ppm and 2.82 ppm for channel catfish and bluegill sunfish. Thus, 4-aminopyridine formulated products do not present a hazard to fish.

As indicated by the Environmental Fate Chapter, residues of 4-aminopyridine in soil are expected to be insignificant. Therefore, terrestrial plants including corn and sunflowers, are not expected to be adversely affected by application of 4-aminopyridine formulated products.

Required Labeling

The following labeling requirements are made on the basis of the available ecological effects data:

Manufacturing 4-aminopyridine:

Do not discharge into lakes, streams, ponds or public waters unless in accordance with an NPDES permit. For guidance, contact your regional office of EPA.

For All Formulations:

For use only by certified applicators or persons under their direct supervision.

This pesticide is toxic to birds and fish. Wildlife feeding on treated bait may be killed.

Do not contaminate water by cleaning of equipment or disposal of waste.

Before application in your area, consult endangered species personnel of the U.S. Fish and Wildlife Service to ensure that endangered and rare bird species are not likely to be adversely affected by use of this product.

For Pre-treated Baits

Do not allow this material to remain in unprotected places after control measures are completed.

For Ready-to-Use Bait Products Containing Greater than 3% (pre-treated particle) 4-aminopyridine and For All Dust Products

Pick up and dispose of dead birds by burial.

For Products Intended for Use at Sanitary Landfills, Cattle Feed Lots, or Nesting and Roosting Sites:

This product must not be applied where nontarget birds feed. Careful observation of birds feeding habits must be made to establish proper feeding locations and to determine that no nontarget birds are feeding on prebait.

Pick up and destroy uneaten bait at the end of each day.

For Products Intended for the Control of Herring Gulls (*Larus argentatus*)

Herring Gulls (*Larus argentatus*) are protected by law and treaty. Both Federal and Staate permits are required to control these birds.

For All Products Intended for Use in Agricultural Crops

Confine treatment to areas 50 feet in from field edge.

Ecological Effects Bibliography

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05003191 Schafer, E.W., Jr.; Brunton, R.B.; Lockyer, N.F.; De Grazio, J.W. (1973) Comparative Toxicity of Seventeen Pesticides to the Quelea, House Sparrow, and Red-Winged Blackbird. Toxicology and Applied Pharmacology 26(1):154-157.

00003965 Schafer, E.W., Jr.; Marking, L.L. (1974) Long Term Effects of 4-aminopyridine Exposure to Birds and Fish. (Unpublished study received Nov 11, 1975 under 11649-15; prepared by U.S. Fish and Wildlife Service, Wildlife Research Center in cooperation with Fish Control Laboratories, submitted by Avitrol Corp., Tulsa, Okla.; CDL:225255-C)

00004037 Starr, R.I.; Cunningham, D.J. (no date) Phytotoxicity. (Unpublished study received Jan 3, 1973 under 1F1013; prepared by U.S. Fish and Wildlife Service, Denver Wildlife Research Center, submitted by Phillips Petroleum Co., Bartlesville, Okla.; CDL:091757-R)

05003440 Starr, R.I.; Cunningham, D.J. (1974) Phytotoxicity, Absorption, and Translocation of 4-aminopyridine in Corn and Sorghum Growing in Treated Nutrient Cultures and Soils. Journal of Agricultural and Food Chemistry 22(3):409-413.

00003985 U.S. Fish and Wildlife Service, Denver Research Laboratory (no date) Toxicity of Avitrol to Bluegill and Channel Catfish at Selected Water Qualities and Temperatures: Table. (Unpublished study received May 18, 1971 under 224-EX-3; prepared in cooperation with La Crosse Fish Control Laboratory, submitted by Phillips Petroleum Co., Bartlesville, Okla.; CDL:122743-F)

Standard Reference

U.S. Environmental Protection Agency (1978) Proposed Guidelines for Registering Pesticides in the United States. Federal Register, 43 (132), 19696.

VI. Toxicology

Toxicology Topical Discussions

The following topical discussions describe available toxicity data on technical 4-aminopyridine and its formulations and state whether the data are adequate for Agency regulatory purposes. Agency accetance depends on the adequacy of test substances used to represent a product on which toxicity data are required and on the adequacy of the toxicity test procedures used to satisfy Agency requirements.

Because 4-aminopyridine ready-to-use bait and dust formulations are dilutions of the technical chemical with foodstuffs, the toxicity of a particular formulation depends directly on the concentration of the active ingredient present in that formulation. Therefore, when no data specific to formulations were available, toxicity categories were based on extrapolation from data available on the technical chemical.

Test procedures in several toxicity tests submitted for 4-aminopyridine did not meet proposed Agency guideline requirements. Some of those tests were determined to be adequate, however, for Agency regulatory purposes. The judgments made are included in the following topical discussions.

Numbers in parentheses next to topical discussion subheadings correspond to the number of the section(s) in the Proposed Guidelines of August 22, 1978 (U.S. Environmental Protection Agency, 1978) which explain(s) the minimum data that the Agency usually requires in order to adequately assess a pesticide's toxicology.

Acute Oral Toxicity (163.81-1)

The minimum data requirement for testing acute oral toxicity (LD_{50}) of 4-aminopyridine is one test on the technical chemical, preferably using the rat.

Technical: Ives (1962, 00004024) conducted a study in which laboratory rats and dogs were administered 4-aminopyridine hydrochloride, in capsule form by gavage. The LD_{50} was 28.7 mg/kg (S.D. = 0.6 mg/kg) for the rat and 3.7 mg/kg (S.D. = 0.6 mg/kg) for the dog; both species showed very steep dose response curves. This study meets Agency requirements for an acute oral toxicity test and is adequate to place technical 4-aminopyridine in Toxicity Category I, indicating a very high acute oral toxicity hazard.

Formulations: Ives (1962, 00004024) conducted a secoond acute oral toxicity study in which a .53% granular formulation was administered to dogs and swine in their feed. The LD_{50} for dogs was 2300 mg of formulation/kg which is equivalent to 12.6 mg of active ingredient/kg. The LD_{50} for the swine was 3400 mg of formulation/kg which is equivalent to 18 mg of a.i./kg. This study does not meet Agency requirements for an acute oral toxicity test because too few animals were used in the experiments. Taken alone, therefore, the results cannot be considered conclusive. However, the data in this study support the results obtained (Ives, 1962, 0004024) with the technical material. The difference between the dog LD_{50} determination (3.7 mg/kg) from the technical material and the dog LD_{50} determination from the .53% granular formulation is most likely due to the route of administration. LD_{50} values are generally higher when substances are administered in feed than when they are introduced directly into the animals' stomachs by gavage. Based on extrapolations from data on the technical chemical, formulations of 4-aminopyridine are assigned to the following Toxicity Categories for acute oral toxicity:

- o Formulations containing 25% or more 4-aminopyridine--Toxicity Category I
- o Formulations containing 2.5% to 24% active ingredient--Toxicity Category II
- o Formulations containing less than 2.5% active ingredient--Toxicity Category III

Acute Dermal Toxicity (163.81-2)

Technical: The minimum data requirement for testing the acute dermal toxicity (LD_{50}) of 4-aminopyridine is one test on the technical formulation, preferably using the albino rabbit. The acute dermal LD_{50} of 4-aminopyridine hydrochloride is 327 mg/kg (S.D. = 54.3 mg/kg) for male rabbits (Ives, 1962, 00004024). Animals exhibited signs of ataxia, hyperpnea, salivation and tremors. No gross pathological changes were noted in any tissues or organs examined. Although data on female rabbits were not submitted, the Agency considers the available data sufficient to assess the acute dermal toxicity of technical 4-aminopyridine. Based on this study, technical 4-aminopyridine is assigned to Toxicity Category II for dermal effects.

Formulations: No data specific to 4-aminopyridine formulations were available for assessing acute dermal toxicity. Based on extrapolation from data available on the technical chemical, formulations of 4-aminopyridine are assigned to the following Toxicity Categories for acute dermal toxicity:

- o Formulations containing 65% or more 4-aminopyridine -- Toxicity Category II.
- o Formulations containing 6.5% to 64% -- Toxicity Category III.
- o Formulations containing less than 6.5% active ingredient -- Toxicity Category IV.

Acute Inhalation Toxicity (163.81-3)

A determination of the acute inhalation toxicity is required to support the registration of a manufacturing use product and a formulated product if:

1) The product is a gas;
2) The product produces a respirable vapor; or
3) 20 percent or more of the aerodynamic equivalent of the product is composed of particulates not larger than 10 microns in diameter.

Neither 4-aminopyridine manufacturing use products nor ready-to-use bait formulations meet any of the conditions listed above. Therefore, no inhalation testing of these products is necessary. Dusts, however, meet condition 3. In order to develop proper labeling, dust formulations must be tested for acute inhalation toxicity. The minimum data requirement is one test, using the albino rat, of a 50% a.i. dust.

Acute Delayed Neurotoxicity (163.81-7)

Acute delayed neurotoxicity data are required if the active ingredient, or any of its metabolites, degradation products, or impurities cause esterase depression or are structurally related to a substance that induces delayed neurotoxicity. 4-aminopyridine does not cause esterase depression nor is it structurally related to a substance that is known to induce delayed neurotoxicity. Therefore no testing is required for the technical formulation or any of its registered products.

Primary Eye Irritation (163.81-4)

The minimum data requirement for evaluating 4-aminopyridine eye irritation potential is one test on the technical chemical, preferably on the albino rabbit.

Technical: One study (Ives, 1962, 00004024) on primary eye irritation was reviewed. In the study, 10 mg of 4-aminopyridine hydrochloride were instilled into the eyes of albino rabbits. At 1 hour, iritis and conjunctival irritation were noted; these irritations disappeared by day 7. Although less 4-aminopyridine than the amount recommended by the Proposed Guidelines (U.S. Environmental Protection Agency, 1978) was instilled into the rabbits' eyes, the Agency considers the data adequate to assign technical 4-aminopyridine to Toxicity Category III for primary eye irritation.

Formulations: No data specific to formulations were available. Based on extrapolation from data available on the technical chemical, all 4-aminopyridine formulations are assigned to Toxicity Category III.

Primary Dermal Irritation (163.81-5)

The minimum data requirement for evaluating the dermal irritation potential of 4-aminopyridine is one test on the technical formulation, preferably on the albino rabbit.

Technical: Ives (1962, 00004024) observed rabbits after 50 mg of 4-aminopyridine hydrochloride were applied to abraded and intact skin. He observed no signs of irritation, either at 24 hours or 72 hours. Although less 4-aminopyridine than the amount recommended by the Proposed Guidelines was applied, the Agency considers the data adequate to assign technical 4-aminopyridine to Toxicity Category IV for primary dermal irritation.

Formulations: Phillips Petroleum Co. (no date, 00004137) submitted a study in which granular 4-aminopyridine (amount unspecified) was applied to the clipped skin of rabbits on 10 consecutive days. Each application remained in place for 18 hours but no signs of irritation were observed. Because the amount of 4-aminopyridine applied to the skin was not specified, this study cannot be considered adequate for assessing the primary irritation potential of 4-aminopyridine formulations. However, it does support data available on the technical chemical. Therefore, based on this study and the data on the technical chemical, 4-aminopyridine is assigned to Toxicity Category IV for primary dermal irritation.

Subchronic Oral Toxicity (163.82-1)

The minimum data requirement for assessing the subchronic oral toxicity of 4-aminopyridine is one test in each of two mammalian species, a rodent and a nonrodent, on the technical chemical.

Technical: No subchronic oral tests on 4-aminopyridine were available. In one 90-day study, (Kohn et al., 1968, 00004026) rats were given dietary levels of 3, 30, and 300 ppm 4-aminopyridine hydrochloride (calculated as free base). No gross or microscopic pathologic findings of significance were noted. In the group given 300 ppm, all surviving animals were hyperirritable to noise and touch throughout the test. No other abnormal behavioral reactions occurred. Blood and urine analyses of rats given the high dose showed no significant changes. Female rats given 300 ppm showed elevated brain weight ($p<0.05$); male rats showed elevated liver weight ($p<0.05$) when given the same dose. This study is an adequate subchronic oral test in rats.

A subchronic study was also conducted on dogs (Cervenka and Vega, 1968, 00004027). The study was informative, although it was conducted for 90 days instead of the desired 180 days. 4-aminopyridine hydrochloride was given in the diet at 0.1, 1.0, and 2.0-3.25 mg/kg/day (corresponding to 200, 2,000 or 4,000 - 6,500 ppm, calculated in terms of the free base). At the highest dose, dogs exhibited salivation and muscular weakness but developed no abnormal lesions. No dose-related trends occurred in mean organ weights, but male and female dogs given the two highest doses showed decreased brain weights. Blood and urine values were comparable in treated and control animals.

In summary, rats and dogs in the 90-day studies showed no significant pathologic changes in any organ or tissue. In both rats and dogs brain weight was affected, but examination of the brain revealed no abnormalities.

Formulations: No significant subchronic oral toxicity effects were observed in tests of the technical chemical. Therefore, non should result from exposure to 4-aminopyridine formulations. No subchronic oral toxicity testing specific to ready-to-use baits or dusts is required.

Dermal Sensitization (163.81-6)
Subchronic 21-Day Dermal Toxicity (163.82-2)
Subchronic 90-Day Dermal Toxicity (163.82-3)

Dermal sensitization data and subchronic dermal toxicity data are required if repeated skin contact with a pesticide is expected under conditions of use. Applicators who handle 4-aminopyridine manufacturing-use products, or any dust or pretreated bait product which falls into Toxicity Category I or II for dermal toxicity, will be required to wear protective clothing, including gloves, thereby greatly reducing the potential for repeated skin contact. Applicators who handle pretreated baits which fall into Category III or IV for dermal toxicity will not be required to wear gloves, since they are unlikely to be exposed to the active ingredient in sufficient quantities for dermal sensitization or subchronic toxicity problems to develop. Because of the lack of significant dermal exposure, no subchronic dermal toxicity or dermal sensitization testing is required for 4-aminopyridine.

Subchronic 90-Day Dermal Toxicity (163.82-3)

Data from a subchronic inhalation toxicity study are required to support the registration of each manufacturing-use product and formulated product which has been identified as toxic from the results of acute inhalation testing and whose use may result in repeated inhalation exposure. Because of the nature of 4-aminopyridine manufacturing-use products and ready-to-use baits, no inhalation exposure to these products is expected. Short term inhalation exposure to dusts may occur if applicators do not wear respirators. However, based on available information on the use pattern of 4-aminopyridine dust products, significant repeated inhalation exposure to dusts is not expected to occur even if respirators are not worn. Therefore, subchronic inhalation toxicity testing is not required.

Subchronic Neurotoxicity (163.82-5)

Data from a subchronic neurotoxicity evaluation are required to support the registration of each manufacturing-use product and formulated product containing an active ingredient which induced neuropathy or delayed neurotoxicity in acute tests. A subchronic neurotoxicity study is not required for 4-aminopyridine because no neuropathy or delayed neurotoxicity was observed in acute tests. In addition, significant repeated exposure to 4-aminopyridine is not expected to occur.

Chronic Feeding (163.83-1)
Oncogenicity (163.83-2)
Reproduction (163.83-4)
Metabolism (163.85-1)

Chronic feeding, oncogenicity, metabolism, and multigeneration reproductive studies are usually required if use of a pesticide is likely to result in repeated human exposure over a significant portion of the human life span or if a use requires a tolerance or an exemption from a tolerance.

Although significant prolonged exposure to handlers and applicators of 4-aminopyridine is unlikely, the fact that 4-aminopyridine has a tolerance of 0.1 ppm for both corn and sunflowers would normally indicate that long term studies are necessary. However, the Agency believes that residue levels in crops resulting from either translocation of 4-aminopyridine to food crops or from the direct application of 4-aminopyridine to growing crops will be lower than the tolerances set (see Residue Chemistry Chapter - Residues in corn and sunflowers). Therefore, because dietary intake of 4-aminopyridine is expected to be negligible and because prolonged human exposure is unlikely, the long-term studies listed above are not required for 4-aminopyridine.

Teratology (163.83-3)

Teratogenic studies on the technical chemical, using two mammalian studies, are required if the pesticide's use requires a tolerance or an exemption from a tolerance or if its use may result in exposure to human females. No significant dietary or chronic exposure to 4-aminopyridine is expected (see Residue Chemistry Chapter and above discussion on long-term studies). In addition, no significant (including short-term) dermal exposure is expected to result from the application of pretreated baits (see Dermal Sensitization Topical Discussion). However, if applicators of 4-aminopyridine dusts do not wear protective clothing, including long sleeves, gloves, and respirators, short-term inhalation exposure and dermal exposure to dusts will occur. Therefore, unless applicators of dust formulations are required, by the label, to wear protective clothing including respirators, the teratogenic potential of 4-aminopyridine must be determined.

Mutagenicity

Mutagenicity testing will be required for 4-aminopyridine unless applicators of dust formulations are required by the label to wear protective clothing including respirators (see above discussion on teratology).

The following studies represent the minimum requirements for data on the potential heritable effects of 4-aminopyridine.

1. A mammalian in-vitro point mutation test.
2. A sensitive sub-mammalian point mutation test. (Bacteria, fungi, insect.)
3. A primary DNA damage test (i.e. sister chromatid exchange or unscheduled DNA synthesis).
4. A mammalian in-vitro cytogenetics test. If this test suggests a positive result, a dominant lethal or heritable translocation test may be required.

After results from these test systems and other toxicology disciplines have been considered, additional testing may be required to further characterize or quantify the the potential genetic risks.

Although the Agency's mutagenic testing requirements are not final, the standards for these tests should be based on the principles set forth therein (43 FR 37336 August 22, 1978). Protocols and choices of test systems should be accompanied by a scientific rationale. Substitutions of test systems for those listed above will be considered after discussion with the Agency.

The requirements should be considered an interim guide and not final Agency policy. However, the Agency does consider the above testing scheme to be a reasonable minimum requirement.

Pharmacological Effects

In Vivo Effects: 4-aminopyridine produced prolonged increases in the blood pressure of cats (Fastier, 1958, 05004214). The cats' blood pressure was increased an average of 50 mm Hg following administration of 1 mg/kg of 4-aminopyridine intravenously. It remained elevated by 20 mm Hg up to 30 minutes after 4-aminopyridine administration. Barbituate hypnosis in mice was antagonized 30% by 5 mg/kg of 4-aminopyridine (Vohra et al. 1969, 05003184). These effects indicate involvement of the autonomic nervous system.

In the rat brain and spinal cord, 4-aminopyridine stimulated release of norepinephrine but not 5-hydroxytryptamine or dopamine (Anden and Leander, 1979, 05003729). 4-aminopyridine did not stimulate norepinephrine by electrical stimulation. This suggests an effect on the electrical conductivity of the nerve membrane.

In Vitro Effects: In isolated skeletal and smooth muscle preparations, 4-aminopyridine increases twitch tension and reverses the nondepolarizing neuromuscular blockade. Inhibition of membrane potassium conductance by 4-aminopyridine prolongs the presynaptic spike, allowing an increase in acetylcholine release at the presynaptic membrane. The mechanism of action of 4-aminopyridine at the neuromuscular junction is calcium-dependent, and it probably acts by affecting calcium permeability of the presynaptic membrane.

Dose-dependent positive inotropic responses (contractions) were produced by 4-aminopyridine in guinea pig ileum (Moritoki et al., 1978, 05003154) and canine tracheal muscle (Kannan and Daniel, 1978, 05003155). The positive inotropic effect of 4-aminopyridine was reduced when treated with a combination of phenoxybenzamine (an alpha blocker) and propranolol (a beta blocker) (Leander et al., 1970, 05003158). When phentolamine, another alpha-blocker, was used instead of phenoxybenzamine, no reduction in the effect of 4-aminopyridine was observed. This suggests that 4-aminopyridine does not have an agonistic effect on alpha-receptors.

In superfused guinea pig ileum, 4-aminopyridine decreased contractile responses stimulated by carbachol by more than 50% (Fastier, 1958, 05004214). Contractile responses were increased in the presence of choline or by anticholinesterase agents such as physostigmine (Al Haboubi et al., 1978, 05006379) and neostigmine (Al Haboubi et al., 1978, 05006379). Atropine, a cholinergic antagonist (Kannan and Daniel, 1978, 05003155, Al Haboubi, 1978, 05006379, Moritoki et al., 1978, 05003154) antagonized the contractile response to 4-aminopyridine. Because initiation and potentiation of contractile responses were blocked by atropine and tetrodotoxin and increased by cholinesterase inhibitors, it is suggested that the effect of 4-aminopyridine is the result of indirect cholinergic action. The action of 4-aminopyridine appears to be Ca^{++}-dependent (Al Haboubi et al., 1978, 05006379). 4-aminopyridine potentiated by eight times the tension of muscle twitch evoked by phrenic nerve stimulation in the presence of tubocurarine (Bowman et al., 1977, 05003160). In the presence of 4-aminopyridine, extremely high doses of curare were required to abolish twitches. These data indirectly support the conclusion that the mechanism of action of 4-aminopyridine is on the presynaptic membrane.

In summmary, 4-aminopyridine selectively blocks membrane potassium conductance in both nerve and muscle. Inhibition of membrane potassium conductance prolongs the presynaptic action potential, resulting in an increase in the amount of neurotransmitter released at the presynaptic membrane. The mechanism of 4-aminopyridine is calcium-dependent, probably acting by increasing the influx of calcium ions during the nerve terminal action potential.

Clinical Effects

4-aminopyridine increases transmitter release from the nerve terminals, probably by increasing calcium permeability of the nerve terminal membrane. 4-aminopyridine has been shown to restore neuromuscular transmission in myasthenia gravis, Eaton-Lambert syndrome, and pancuronium-lincomycin neuromuscular blockage in man.

In six patients with myasthenia gravis, intravenous adminstration of 10 to 20 mg of 4-aminopyridine caused a marked improvement in clinical status (Lundh et al., 1979, 05003494). Similar improvements were reported for two Eaton-Lambert syndrome patients (Lundh et al., 1977, 05004217, Agoston et al., 1978, 05003178). Electrophysiological examination before and after intravenous injection of 4-aminopyridine revealed some improvement in all eight patients discussed above. Results suggest that 4-aminopyridine may be a valuable drug in the treatment of myasthenia gravis and myasthenic syndrome, sometimes associated with Eaton-Lambert syndrome.

Clinical Side Effects

In six adult patients with myasthenia gravis, intravenous administration of 10-20 mg of 4-aminopyridine produced perioral paraesthesia within seconds (Lundh et al., 1979, 05003494). The paraesthesia disappeared within a few minutes of 4-aminopyridine administration.

In a clinical study of 57 surgical patients, no signs of central nervous system stimulation were observed after single intravenous doses of 0.15, 0.35, or 0.50 mg/kg of 4-aminopyridine (Miller et al., 1979, 05004966). After a single intravenous administration of 10 to 20 mg, four of six patients experienced a temporary sensation of unsteadiness during walking, lasting 0.5 - 2 hours (Lundh et al., 1979, 05003494). However, no objective signs of disturbed gait, posture, or coordination were observed.

Miller et al. (1979, 05004966), Lundh et al. (1977, 05004217), and Lundh et al. (1979, 05003494) reported no significant changes in blood pressure or heart rate after administration of 4-aminopyridine. Agoston et al. 1978, (05003178) reported a slight decrease in heart rate but no changes in blood pressure in an Eaton-Lambert syndrome patient given up to 120 mg/day of 4-aminopyridine for 120 days (Lundh et al., 1977, 05004217). No changes in routine blood tests of liver or kidney function were observed in this patient.

These studies demonstrate that intravenous administration of single doses of 4-aminopyridine at 0.5 mg/kg or repeated dosing of up to 120 mg/day for 20 days produced no adverse effects in humans.

DISCIPLINARY REVIEW

Toxicology Profile
Toxicology Hazard Assessment
Data Gaps
Required Labeling

Toxicology Profile

Technical 4-aminopyridine

The very low acute oral LD_{50} in both laboratory rats (28.7 mg/kg) and dogs (3.7 mg/kg) indicate a high acute oral toxicity in humans. The acute dermal toxicity in male rabbits (LD_{50} = 327 mg/kg) suggests a moderate dermal toxicity in humans. Technical 4-aminopyridine is expected to produce only mild, short-term eye irritation in humans, based on studies conducted with rabbits. Mild eye irritation lasting less than 7 days was noted when this compound was instilled into rabbit eyes. Technical 4-aminopyridine is not expected to cause skin irritation in humans. No sign of skin irritation was noted when 4-aminopyridine was applied to intact and abraded rabbit skin.

Adequate subchronic 90-day oral toxicity data were available for technical 4-aminopyridine. No significant pathologic changes in any organ or tissue and no compound-related effects in blood or urine in rats and dogs were noted. However, at high doses (2.0-3.25 mg/kg/day) brain weight in dogs was affected, although examination of the brain revealed no abnormalities. The no-observable-effect level (NOEL) was 3 ppm in rats and 200 ppm (.1 mg/kg/day) in dogs.

4-aminopyridine Formulations

Very little data specific to any of the formulations of 4-aminopyridine were available. Based on extrapolation from data available on the technical compound, formulations of 4-aminopyridine are assigned to the following Toxicity Categories:

Acute Oral Toxicity:

- o Formulations containing 25% or more 4-aminopyridine--Toxicity Category I
- o Formulations containing 2.5% to 24% active ingredient--Toxicity Category II
- o Formulations containing less than 2.5% active ingredient--Toxicity Category III

Acute Dermal Toxicity:

- o Formulations containing 65% or more 4-aminopyridine--Toxicity Category II
- o Formulations containing 6.5% to 64% active ingredient--Toxicity Category III
- o Formulations containing less than 6.5% active ingredient--Toxicity Category IV

Primary Eye Irritation: All formulations--Toxicity Category III

Primary Dermal Irritation: All formulations--Toxicity Category IV

No data were available for assessing the acute inhalation toxicity to humans of 4-aminopyridine dust formulations.

Hazard Assessment

4-aminopyridine Formulations

The 'Exposure Profile' which appears in the Environmental Fate Chapter indicates that there is little chance of oral exposure to 4-aminopyridine formulations, except through accidental ingestion. Dietary exposure from residues in corn and sunflowers is expected to be insignificant. Accidental ingestion of 4-aminopyridine can result in serious poisoning and, in some cases, death. The severity of the poisoning is dependent upon the concentration of active ingredient in the formulation swallowed.

No inhalation exposure to ready-to-use baits will occur, due to the nature of these formulations. Inhalation of dusts may occur, however, if applicators do not wear respirators. No inhalation toxicity hazard assessment can be made for 4-aminopyridine dusts because of the lack of data. Similarly, the potential for teratogenic or mutagenic effects resulting from inhalation exposure cannot be determined because of a lack of data.

Because the applicator will be required to wear gloves, there should be no hazards resulting from dermal exposure to any 4-aminopyridine dust or pretreated bait product which falls into Toxicity Category I or II for dermal toxicity. Applicators who handle pretreated baits which fall into Category IV will not be required to wear gloves and may be exposed on a short-term basis to very small amounts of 4-aminopyridine. The hazard is slight, however, since such products have very low dermal toxicities. Accidental occular exposure may occur while handling dusts. Eye exposure to either the 50% or the 25% dust formulation is expected to produce only mild, short-term eye irritation. Since chronic exposure to 4-aminopyridine for either the applicator or the public will not occur, no oncogenic reproductive or general chronic effects are expected to result from use of 4-aminopyridine products.

Data Gaps

The following are gaps in the Toxicology data base needed to adequately support a Registration Standard for 4-aminopyridine. Listed after each gap, is the section in the proposed Guidelines (U.S. Environmental Protection Agency, 1978) which describes that type of study and when it is required.

Technical 4-aminopyridine	Guideline Section
No data requirements	
4-aminopyridine Dusts	
Acute Inhalation toxicity study	163.81-3

Registrants of dust formulations must agree to provide or cite the following studies, OR to adhere to label requirements for protective clothing discussed in the required Labeling Section of this chapter.

Teratogenicity (2 species)	163.83-3
Mutagenicity	163.84-1, 2, 3, 4

Required Labeling

Each 4-aminopyridine product must bear label statements appropriate to the Toxicity Categories assigned to that product for each acute effect (refer to 162.10 of 40 CFR, 1978) with the following exception: Labels on all 4-aminopyridine dust products, regardless of the Toxicity Categories assigned, must require applicators to wear protective clothing including long sleeves, gloves, and respirators.

To help prevent accidental oral ingestion, dust product labels must also bear the requirement, "Bait materials resembling human food must be altered in form by crushing, balling, or pelleting so that they are not readily recognizable as human food."

Despite precautions, accidental oral ingestion may still occur. Consequently, the following statement of emergency treatment must be included on the label of all 4-aminopyridine manufacturing-use, and formulated products:

> IF SWALLOWED: If the patient is unconscious, maintain breathing and heart beat (CPR: cardiopulmonary resuscitation). Contact your local Poison Control Center, hospital or physical immediately.
>
> If patient is conscious, induce vomiting with syrup of ipecac (if not available stimulate the back of the throat with finger). Never give anything by mouth to an unconscious person! Contact you local Poison Control Center, hospital or physician immediately.

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VII. Residue Chemistry

Topical Discussions

The Proposed Guidelines for residue chemistry have not been published. Accordingly there are no citations for guidelines corresponding to the types of residue chemistry data normally required to support individual registrations. In general, however, the Agency must have sufficient data for each proposed product to be assured that the residues of the parent chemical and its metabolites have been quantitatively and qualitatively identified.

Plant Metabolism of 4-aminopyridine:

Data are required to examine the metabolism of 4-aminopyridine in the crop to which it is applied. The available information on this topic is summarized by crop.

Corn: The amount of information available on the metabolism of 4-aminopyridine in plants is limited. There is one report in the published literature (Starr and Cunningham 1975, 05003202) regarding the degradation of 4-aminopyridine in corn. Young corn plants were exposed to 10 ppm of 4-aminopyridine in nutrient solution for 7 days. TLC-autoradiography of the acetone extracts showed no ^{14}C-radioactivity other than parent compound in roots or shoots. A study (Starr and Cunningham 1966, 0004039) of the absorption of 4-aminopyridine from soil or nutrient solution by variously aged corn plants demonstrated that older plants absorb less ^{14}C-4-aminopyridine than younger plants. 2-month old corn plants absorbed much less ^{14}C-radioactivity from soil at 10 ppm than from nutrient solution. Corn plants at three months showed that detectable radioactivity in an ear of corn and in the uppermost 2 feet of stalk resulted from exposure to nutrient solution at 5 ppm. The first three 12-inch sections of the stalk contained 1.4, 0.074, and 0.004 ppm of ^{14}C-equivalent to 4-aminopyridine respectively. Nutrient solution exposure is much greater than exposure under field conditions. Therefore, residues of 4-aminopyridine in corn under field treatments are expected to be considerably lower.

In summary, the only residue of 4-aminopyridine found in corn plants was the compound itself. No metabolites of 4-aminopyridine were detected. No ^{14}C-radioactivity was detected in corn grain after nutrient solution exposure. Based upon this information, the low application rate, and the field residue data discussed below, residues of 4-aminopyridine are not expected in corn grain under normal use conditions.

Sunflowers: There are no available reports of the metabolism of 4-aminopyridine in sunflower plants. Cunningham (1975, 00004088) studied the absorption of 4-aminopyridine by sunflower plants from soil treated at an exaggerated rate of 20 applications. The concentration in the soil was 0.02 ppm. However, during the 3 weeks of growth, there was no observable difference between treated and control plants in the amount of ^{14}C-radioactivity in sunflower leaves, stems and stalks, and flower plus leaves. This information indicates that residues of 4-aminopyridine or its metabolites would not be expected in sunflower plants under field conditions.

Other Plants: The metabolism and degradation of 4-aminopyridine in sorghum plants were reported by Starr and Cunningham (1975, 05003202). Acetone extracts of young sorghum plants exposed to 5 ppm 4-AP in nutrient solution for one week followed by one week without exposure, contained 3 distinct ^{14}C- containing degradation products. The three degradation products contained from 0.5% to 4.4% of the recovered ^{14}C [recovery ravage 83% to 95%]. The degradates were not identified or characterized other than by reported RF values in a specific TLC procedure. More than 90% of the recovered ^{14}C was in the parent compound, as shown by TLC-autoradiographic procedures. When more mature plants were tested, only low levels of unidentified ^{14}C-radioactivity were reported in sorghum seeds and heads, following nutrient solution exposure at 5 ppm. This study suggests that some 4-aminopyridine plant metabolism occurs, since ^{14}C-radioactivity was less easily recovered from older plants than from younger plants.

Animal Metabolism:

Data on animal metabolism are required if residues are found in animal food or feed items. Sullivan (1970, 00004030), reported that *in vitro* beef and chicken liver homogenates showed no observable degradation of 4-aminopyridine during 24 hours of incubation. Although this study would not fulfill an animal metabolism data requirement, additional data are not needed since residues of 4-aminopyridine are not expected in animal food and feed items (see above).

Analytical Methods:

Because 4-aminopyridine is used on crops, an analytical method for detecting 4-aminopyridine residues in treated crops is required. The method must be valid and specific for 4-aminopyridine, without interference from other pesticides which may be applied to these crops.

Several methods for the extraction, cleanup, and estimation of 4-aminopyridine concentrations have been reported. One method (Peterson, 1971, 05003193) was considered to be inadequate due to lack of information regarding the fortification samples. However, further development and modification of Peterson's method were reported by Sullivan (1970, 00004030) and Phillips Petroleum Company (no date, 00004016). These improvements make this method valid for the extraction, cleanup, and estimation of residues of 4-aminopyridine in treated corn. The method is as follows:

Fresh whole corn plant is chopped up into small particles and air dried to constant weight. An aliquot is blended with acetonitrile containing 3% ammonium hydroxide. After filtration, the acetonitrile solution is shaken just to dryness. The residue is transferred to a separatory funnel which is shaken vigorously for 5 minutes with n-butyl acetate and 0.1 N HCl, and the phases are allowed to separate. The aqueous phase is transferred to another separatory funnel, and is shaken again with n-butyl acetate. The phases are allowed to separate and both n-butyl acetate phases are discarded. The aqueous phase is transfered to a third separatory funnel. It is adjusted to pH 11 with 10% sodium hydroxide and n-butyl acetate is added. The phases are allowed to separate and the aqueous phase is discarded. The organic phase is passed through anhydrous sodium sulfate with additional n-butyl acetate. The solvent is reduced just to dryness and the residue is quantitatively transferred to a graduated centrifuge tube with redistilled acetone. The acetone solution is reduced to 1 ml or less for gas chromatography under the following conditions:

Column -- Chromosorb 103
Temperature -- 228°C
Helium carrier flow -- 15 at 40 psi = about 100 ml/min
Sensitivity -- 1 x 30
Inlet -- 250°C
Transfer -- 250°C
Furnace -- 900°C
Detector -- Nitrogen conductivity detector

The minimum level detectable by this procedure is 10 nanograms or 0.1 ppm for 100 gram samples (fresh weight). The recovery of 4-aminopyridine from 4 control samples fortified at 0.1 ppm ranged from 70% to 80 %, while at 0.4 ppm the recovery in one control sample was 86% (Sullivan, 1970, 00004030).

The analytical method described above was used to report the residues of 4-aminopyridine in field treated samples of corn. It was also the method published in the Pesticide Analytical Manual, Vol. II, for the determination of 4-aminopyridine residues in corn. The method has been subjected to thorough analytical research for accuracy and sensitivity in EPA laboratories.

The same method is considered adequate for residues of 4-aminopyridine in sunflower seeds although a high degree of scatter of recovery values has been reported (Copeland, 1972, 00004050). Attempts to modify the method to improve the recovery from sunflower seeds were reported by Peterson (1974, 00004048; 1975, 05003192). Due to the high content of oil and cellulose material, the modifications were thought to be necessary to allow the extraction of 4-aminopyridine from sunflower seeds. These modifications are described below:

Seeds and plant tissues are ground to 30 mesh and extracted with n-butyl acetate and sodium hydroxide. The 4-aminopyridine is partitioned from n-butyl acetate into water under acidic conditions and is cleaned up by passing through a weakly acidic cation exchange resin (Amberlite IRC-50) using hydrochloric acid as regeneration solvent. The residue is repartitioned between n-butyl acetate and water containing either sodium hydroxide or hydrochloric acid. The residue is analyzed on GLC using flame ionization detection or electrolytic conductivity detector. The GLC column material is 3% Carbowax 20M and 0.1% potassium hydroxide on Chromosorb 750. The lower limit of detector linearity is 10 nanograms. Recovery is reported at 50% to 70%.

In addition to the gas liquid chromatographic detection system, procedures for TLC identity confirmation and semiquantitative estimation of 4-aminopyridine residues are reported by Sullivan (1970, 00004007; 1970, 00004030), Starr (no date, 00004126), Schafer and Starr (1969, 00004011), and Phillips Petroleum Company (no date, 00004029).

Residue Data -- Crops:

Data on 4-aminopyridine concentrations in treated crops are required to assure that residues are below tolerance values under actual field conditions. Field residue data are expected to reflect the residues resulting from the registered uses in regard to dosage rates, modes of application, numbers and timing of treatments, formulations used and geographical areas.

Field Corn: One valid study (Sullivan, 1970, 00004030) reported traces of 4-aminopyridine in field corn receiving up to 5 applications of a 1 pound per acre treatment. Traces of 4-aminopyridine in whole corn plants were reported to be less than the minimum detectable residue, 0.1 ppm. There were no differences between the control samples and treated samples.

Sweet Corn: A report of uncertain validity (Peterson, 1974, 00004100), showed corrected residues of 4-aminopyridine at 0.03 ppm maximum in ears of sweet corn. The accuracy of this information cannot be determined because the analytical method was not adequately described.

Sunflowers: There is one report of residue data for 4-aminopyridine in sunflowers receiving both label rates and exaggerated dosages, (USDI, no date, 1015-002-01). At label rates of up to 5 applications, there were no detectable differences between control and treated values. All residue values were less than 0.01 ppm. At exaggerated rates totaling 12.6 pounds of bait per acre in 13 treatments, treated seed samples showed 0.05 ppm of 4-aminopyridine while control samples showed 0.008 ppm.

Estimated Residues in Corn and Sunflowers: In addition to residue data for corn and sunflowers, a variety of calculations or estimates have been made of the residues of 4-aminopyridine that would be expected based on application of active ingredient at the rates indicated on product labels. These calculations are based upon the characteristics of the formulated product and use pattern. The formulated product is applied as a heterogenous mixture of 1% (by weight) treated bait particles and 99% (by weight) untreated bait particles. The treated bait particles contain 3%, by weight, active ingredient. The bait formulation applied contains 0.03%, by weight, 4-aminopyridine. At one pound of bait per acre, per treatment, the amount of active ingredient 4-aminopyridine applied to the crop is 0.0003 lbs per acre.

One report (Phillips Petroleum Company, no date, 00003993) stated that the yield of corn and fodder is 40,000 pounds per acre. Based on this assumption and three applications of 0.0003 pounds active ingredient per acre, the maximum concentration of 4-aminopyridine in corn and grain would be 0.0225 ppm if all the applied 4-aminopyridine were absorbed and translocated. However, testimony presented (Phillips Petroleum Company, no date, 00004017) contended that 80% to 95% of the bait granules reach the ground. Assuming that 10% of the particles lodged in the plant during three applications, the average residue in corn grains and fodder would be 0.0023 ppm.

Another report (Phillips Petroleum Company, no date, 00004022) estimated from particle weight and plant yield per acre that the concentration of 4-aminopyridine in a corn plant would be 6.6×10^{-7} g/g of corn plant if one active treated particle lodged in one corn plant weighing 2.5 pounds.

Similar estimates were made for sunflower seed, based upon yield of seed and plants per acre. Assuming 3 and 4 applications, residues in sunflower plants would be 0.0225 ppm in good sunflower crops (40,000 pounds of plants per acre) and 0.052 ppm in poor crops (23,000 pounds per acre) (Avitrol, no date, 00004049).

A study (Swindle, 1973, 00004039) was conducted to observe the actual number of bait granules lodging in sunflower seed heads or other portions of the plant. Calculations based on the maximum observed number of granules per acre, estimated the residues of 4-aminopyridine in sunflower seeds to be 0.011 ppm, assuming complete adsorbtion and translocation.

This information, together with plant metabolism data, the estimates of residues, and the actual residue data, provide sufficient information on residues of 4-aminopyridine in corn and sunflower seeds. Based upon these data, residues of 4-aminopyridine at method sensitivity (0.1 ppm) are not expected in either corn or sunflowers.

Residue Data -- Processed Commodities:

Data on residues in processed commodities are required if residues are found in the raw agricultural commodity. There are no data available for residues of 4-aminopyridine in processed commodities. However, since residues of 4-aminopyridine do not occur in the raw agricultural commodities (corn, corn fodder and forage, and sunflower seeds), residues of 4-aminopyridine should not occur in processed commodities derived from these raw agricultural products. Therefore, residue data on processed commodities are not required.

Residue Data -- Meat, Milk, Poultry, and Eggs

Data on residues in meat, milk, poultry, and eggs are required if residues are found in animal food or feed items. Based upon residue data on agricultural commodities, significant residues of 4-aminopyridine are not expected to occur in animal food or feed items. Residues of 4-aminopyridine would not be expected in meat, milk, poultry or eggs from animals consuming feed or food items treated with 4-aminopyridine according to label directions. Therefore, data on residues in meat, milk, poultry and eggs are not required to support currently registered uses of 4-aminopyridine.

DISCIPLINARY REVIEW
Residue Chemistry Profile
Tolerance Reassessment
Data Gaps
Required Labeling

Residue Chemistry Profile

At the sensitivity of the method no residues of 4-aminopyridine are likely to be found in corn grain, corn fodder and forage, sweet corn (including popcorn) or sunflower seeds when products are used according to label directions. In addition, calculation of maximum possible residues in these commodities based on the low dosage rates indicates that residues should not result from the label maximums of five applications per year for sunflowers and four applications per year for corn. Since no residues of 4-aminopyridine at method sensitivity are expected in the raw agricultural products, no data are needed for processed commodities or for meat, milk, poultry or eggs.

Available plant metabolism data indicate that some metabolism occurs, with three metabolites isolated (but not identified or characterized) in sorghum plants. No metabolites were found in corn. 4-aminopyridine is absorbed and translocated in corn plants from nutrient solution, but less so from soil. Based on this absorption, translocation and metabolism information, plant uptake of 4-aminopyridine is not expected to be significant in corn and sunflowers.

There were no available studies of animal metabolism of 4-aminopyridine. When 4-aminopyridine was studied *in vitro* in beef and chicken liver homogenate systems, there was no observable metabolism. These data would not fulfill an animal metabolism data requirement, but additional data are not needed because 4-aminopyridine residues are not expected in animal food and feed items.

Tolerance Reassessment

The Theoretical Maximum Residue Contribution (TMRC) for 4-aminopyridine in corn (all types) and sunflower is 0.0038 mg/day for a diet of 1.5 kg. This amount is 4.23% of the Acceptable Daily Intake which is 0.0015 mg/kg/day. In the reassessment of this tolerance, calculations were based upon the level of detection, as were the original tolerances. The Agency does not expect the Average Daily Intake to result in any unsafe levels of 4-aminopyridine in the human diet.

Data Gaps

There are no residue chemistry data requirements for non-food uses of 4-aminopyridine, nor are there any generic residue chemistry data gaps resulting from food uses of 4-aminopyridine at present. The registration/tolerance data requirements for the food uses on corn and sunflowers have been satisfied. Uses of 4-aminopyridine on raw agricultural commodities other than corn and sunflowers would require a validated analytical method, residue data and plant metabolism data. If residues of 4-aminopyridine were to be found in raw agricultural commodities other than corn and sunflowers, data on residues of 4-aminopyridine in meat, poultry and eggs would be required, including identification of the animal metabolites of 4-aminopyridine.

Required Labeling

Labeling of 4-aminopyridine products must bear a warning or restriction against use, storage, or disposal of a 4-aminopyridine formulation in a manner likely to result in contamination of human food items. The bait formulations intended for use on corn and sunflowers should be limited to a maximum of five applications per crop season for sunflowers and four applications per crop season for corn. The specific labeling restrictions for the pretreated bait formulations necessary to prevent contamination of human or animal foods are:

For all products

Do not use where food (grain or meat) might become contaminated.

Do not contaminate water, food or feed by storage or disposal.

For pretreated baits

Do not feed to livestock or poultry.

Do not mix with grain for livestock or poultry feed.

For products intended for use in cattle feed lots

Keep treated bait off the ground, out of reach of cattle.

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VIII. Regulatory Rationale

Data Gaps

Physical and chemical properties data are required for the registration or reregistration of all 4-aminopyridine manufacturing-use and formulated products so that the Agency can characterize each pesticide. Because 4-aminopyridine is a minor use pesticide with an annual production of less than 350 pounds, the following ecological effects and environmental fate studies are not required:

- ° acute toxicity studies on coldwater fish and aquatic invertebrates
- ° a hydrolysis study
- ° an activated sludge study

Study on the fate of 4-aminopyridine in soil are not required because, based on available information on the use patterns of 4-AP end-use products, 4-aminopyridine residues in soil are not expected to reach significant levels. Certain chronic toxicology studies are not required becasue of the following:

1) The use pattern is not expected to result in repeated exposure over a significant portion of the human life span.
2) Although 4-aminopyridine has a tolerance of 0.1 ppm for both corn and sunflowers, human dietary intake from consumption of these crops is expected to be negligible.

In order to develop proper labeling, acute inhalation toxicity data are required for the registration or reregistration of all dust products. Because of the possibility of short-term exposure, teratology and mutagenicity data will be required if applicators of dust products are not required, by the label, to wear protective clothing, including long sleeves, gloves, and respirators.

Products to be Covered Under This Standard

Manufacturing-Use Products

Having considered all the available information on 4-aminopyridine manufacturing-use products, the Agency has determined that manufacturing-use 4-aminopyridine does not cause unreasonable adverse effects with proper label directions and precautions. Therefore, the Agency will accept for registration or reregistration manufacturing-use products with any percentage of 4-aminopyridine so long as inert ingredients greater than 1.0%, by weight of the total product, consist of food or feedstuffs only.

Formulated Products

This Standard covers only 'ready-to-use bait' and 'dust' type formulations whose inert ingredients consist only of food or feedstuffs. Products containing other inert ingredients could have significantly different properties, and products in forms other than dusts or ready-to-use baits would have significantly different application methods not considered by data available on the currently registered products. Additional data pertaining to the product chemistry, environmental fate, toxicology, residue chemistry and ecological effects of new formulation types and their application methods may be needed to support the registration of such products.

Available data are insufficient to adequately determine the hazards to humans and wildlife from pretreated bait or dust products with uses other than those currently registered, including use of ready-to-use baits on additional crops. Because such uses could result in increased exposure and in higher 4-AP residue levels in soil and crops, additional environmental fate, residue chemistry and toxicology data would be required to support such uses. Specifically, additional residue chemistry data would be required to establish tolerances for crops other than corn or sunflowers. The available residue chemistry data are sufficient to establish tolerances only for corn and sunflowers. 4-aminopyridine ready-to-use baits may be applied at the rate of up to .0144 ounces active ingredient per acre on the treated portion of a field maximum of four times per year for corn and a maximum of five times per year for sunflowers without exceeding the established tolerances.

Hazards to Wildlife

Manufacturing-Use Products

To prevent unauthorized disposal of 4-aminopyridine, all manufacturing-use 4-aminopyridine products must carry the following warning on the label:

> Do not discharge into lakes, streams, ponds, or public waters unless in accordance with an NPDES permit. For guidance contact your regional office of EPA.

Formulated Products

Although currently registered 4-aminopyridine ready-to-use baits and dust products are potentially hazardous to wildlife, the Agency considers these products suitable for registration because regulatory actions will help prevent nontarget wildlife exposure and unnecessary target bird mortality. To reduce the potential for unreasonable adverse effects on wildlife, all 4-aminopyridine products will be classified as restricted use pesticides for use only by certified applicators or persons under their direct supervision. In addition, formulated products will be restricted to the following percentages of active ingredient and dilution ratios. Ready-to-use bait formulations must not exceed 3.0% 4-aminopyridine per treated granule diluted to .03% 4-aminopyridine per total product when registered for use in agricultural crops. Ready-to-use baits must not exceed 0.5% 4-aminopyridine when registered to control house sparrows, cowbirds, blackbirds, or pigeons in the area of nesting and roosting sites, or 1.0% 4-aminopyridine when registered to control starlings in cattle feedlots, or crows near nesting and roosting sites. Dust formulations must not exceed 50% 4-aminopyridine when registered to control starlings in cattle feedlots, or 25% 4-aminopyridine when registered to control herring gulls near nesting and roosting sites and at sanitary landfills. Dilution of bait before application should be no less than the following:

- 1 part treated bait to 9 parts untreated bait for pretreated baits used to control pigeons at nesting and roosting sites, and for pretreated bait and dust formulations used in cattle feedlots.
- 1 part treated bait to 10 parts untreated bait for dust formulations used to control herring gulls at sanitary landfills and at nesting and roosting sites.

The 4-aminopyridine concentrations and the dilution ratios noted for the various formulations reflect the maximum concentrations of active ingredient and the minimum dilution ratios of currently registered products. Available ecological effects data indicate that unnecessary target bird mortality, as well as an increased hazard to nontarget wildlife would result if products contained higher percentages of 4-aminopyridine or if dilution ratios were lowered.

The following label statements, in addition to the restrictions discussed above, will help reduce exposure to nontarget birds:

For pretreated baits applied to agricultural crops:

- Before application in your area, consult endangered species personnel of the U.S. Fish and Wildlife Service to ensure that endangered and rare bird species are not likely to be adversely affected by use of this product.
- Do not allow bait to remain in unprotected places after control measures are completed.
- Confine treatment to areas 50 feet in from field edge.

For products used at sanitary landfills, cattle feedlots and nesting and roosting structures:

- This product must not be applied where nontarget bird species feed.
- Careful observation of bird habits must therefore be made to establish proper feeding locations and to determine that no nontarget bird species are feeding on prebait.

Label directions to "Pick up and dispose of dead birds by burial" on all dust products, and on ready-to-use bait products containing greater than 3.0% 4-aminopyridine per treated granule, should reduce the potential for secondary poisoning of predatory wildlife. The label directions "Do not contaminate water by cleaning of equipment or disposal of wastes" should help eliminate fish and aquatic organism exposure to significant quantities of 4-aminopyridine.

Hazards to Humans and Domestic Animals

Ready-to Use Bait and dust Products

All 4-aminopyridine products will be classified as restricted use pesticides and will be handled only by licensed applicators who can be expected to comply with label precautions, and with directions to wear protective clothing. This should greatly reduce the potential for accidental exposure to 4-AP formulated products.

In addition, the following warnings will be included, where appropriate, on product labels to reduce the risks from particular routes of exposure:

For accidental oral exposure to all products:

- Do not use where food (grain or meat) might become contaminated.

For accidental oral exposure to dust products:

- Bait materials resembling human food must be altered in form by crushing, balling, or pelleting so that they are not readily recognizable as food.

For domestic animal exposure to pretreated bait products:

- Keep bait off the ground and out of reach of cattle.
- Do not feed to livestock or poultry.
- Do not mix with grain for livestock or poultry.

For domestic animal exposure to dust products:

- Keep away from livestock, poultry and pets.

APPENDIX A: CHEMICAL DATA SHEET

Chemical Abstracts Chemical Names:

4-Aminopyridine

Other Chemical Names:

gamma-aminopyridine
p-aminopyridine
4-pyridinamine
4-pyridylamine

Structural Formula:

Molecular Formula:

$C_4H_6N_2$ free base

$C_5H_7N_2Cl$ hydrochloride salt

Molecular Weight: 94.11 free base
130.58 hydrochloride salt

Chemical Abstracts (CAS) Registry Number:

504-24-5

Approved Common Name: There is no approved common name at this time

Other Common Names, Trade Names, or Codes:

Avitrol 200
Phillips 1861
4-AP
WLN: T6NJ DZ

APPENDIX B: SUMMARY OF LABEL INGREDIENT STATEMENTS

Three companies, Avitrol, Huge, and Woodbury, are the producers of the 26 registered end-use products now on the market. Nine of these products display the complete ingredient statement of the labels:

1. Huge Company: EPA Registration Number 2270-256

4-aminopyridine	0.05 %
Mixed grains*	99.931
HCl	0.019

*Mixture of 1/3 cracked corn, 1/3 whole wheat, and 1/3 milo.

2. Avitrol Corporation: EPA Registration Number 11649-2

4-aminopyridine	1.0 %
Pelletized feed	98.62
HCl	0.19

3. Avitrol Corporation: EPA Registration Number 11649-3

4-aminopyridine	0.5 %
Sorghum	99.31
HCl	0.19

4. Avitrol Corporation: EPA Registration Number 11649-4

4-aminopyridine	0.5 %
Mixed grains	99.31
HCl	0.19

5. Avitrol Corporation: EPA Registration Number 11649-5

4-aminopyridine	0.5 %
Corn	98.62
HCl	0.38

6. Avitrol Corporation: EPA Registration Number 11649-6

4-aminopyridine	0.5 %
Corn Chops	99.31
HCl	0.19

7. Avitrol Corporation: EPA Registration Number 11649-7

4-aminopyridine	0.5 %
Corn	99.31
HCl	0.19

8. Avitrol Corporation: EPA Registration Number 11649-8

4-aminopyridine	1.0 %
Corn	98.62

HCl	0.38

9. Avitrol Corporation: EPA Registration Number 11649-9

4-aminopyridine	0.8	%
Corn chops	79.1	
Peanut butter	19.8	
HCl	0.3	

Guide to Use of This Bibliography

1. Content of Bibliography. This bibligraphy contains citations of all the studies reviewed by EPA in arriving at the positions and conclusions stated elsewhere in this standard. The bibliography is divided into 3 sections: (1) citations that contributed information useful to the review of the chemical and considered to be part of the data base supporting registrations under the standard, (2) citations examined and judged to be inappropriate for use in developing the standard, and (3) standard reference material. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions, and the published technical literature.

2. Units of Entry. The unit of entry in this bibliography is called a "study." In the case of published materials, this corresponds closely to an article. The Agency has sought to identify documents at a level parallel to a published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes or review, and can be described with a conventional bibliographic citation. The Agency has attempted also to unite basic documents and commentaries upon them, treating them as a single study.

3. Identification of Entries. The entries in this bibliography are sorted by author, date or document, and title. Each entry bears, to the left of the citation proper, an eight digit numeric identifier. This number is unique to the citations, and shuld be called the "Master Record Identifier," or "MRID." It is not related to the six digit "Accession Number" which has been used to identify volumes of submitted data; see paragraph 4(d) below for a further explanation. In a few cases, entries added to the bibliography late in the review may be preceded by a nine-character temporary identifier. This is also to be used whenever a specific reference is needed.

4. Form of the Entry. In addition to the Master Record Identifier (MRID), each entry consists of a bibliographic citation containing standard elements followed, in the case of materials submitted to EPA, by a description of the earliest known submission. The bibliographic conventions used reflect the standards for the American National Standards Institute (ANSI), expanded to provide for certain special needs. Some explanatory notes of specific elements follow:

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    b. Document Date. When the date appears as four digits with no question marks, the Agency took it directly from the document. When a four-digit date is followed by a question mark, the bibliographer deduced the date from evidence in the document. When the date appears as (19??), the Agency was unable to determine or estimate the date of the document.

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   (1) Submission Date. Immediately following the word 'received' appears the date of the earliest known submission.

   (2) Administrative Number. The next element, immediately following the word 'under,' is the registration number, experimental permit number, petition number, or other administrative number associated with the earliest known submission.

   (3) Submitter. The third element is the submitter, following the phrase 'submitted by.' When authorship is defaulted to the submitter, this element is omitted.

   (4) Volume Identification. The final element is the trailing parenthesis identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol 'CDL,' standing for "Company Data Library." This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume. For example, within accession number 123456, the first study would be 123456-A; the second, 123456-B; the 26th, 123456-Z; and the 27th 123456-AA.

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